to, a compound of the present invention in combination with: other (e.g., those other than inhibitors of the present invention) **HIV protease inhibitors** (e.g. Ro 31-8959, SC 52151, **A-77003**, **A-80987**, A-84538 and L-737,524); nucleoside and non-nucleoside reverse transcriptase inhibitors preferably nucleoside reverse transcriptase inhibitors such as AZT, DD1, d4T, DDC, 3TC, or PMEA, and non-nucleoside reverse transcriptase inhibitors such as nevirapine, pyridinones (e.g. L-697,661), BHAPs (e.g. U-90152), alpha-APA derivatives (e.g., R 18893) and TIBO derivatives (e.g. R82913); inhibitors of tat such as RO24-7429; drugs which inhibit binding of the virus to CD.sub.4 receptors; inhibitors of RNase, integrase, or rev; and immunomodulators such as IFN-.alpha. (.alpha.-interferon).

DETD The antiviral activity of the retrocarbamate protease inhibitors of the present invention was evaluated by a microculture method which determines the increase in cell viability of an infected culture when a drug is added. The assay depends on the **metabolic** reduction of tetrazolium reagent by viable cells to yield a soluble colored formazan product.

=> d his

(FILE 'HOME' ENTERED AT 08:25:40 ON 12 NOV 1997)

FILE 'CAPLUS, EMBASE, MEDLINE, BIOSIS, USPATFULL' ENTERED AT 08:26:20 ON 12 NOV 1997

L1	415	FILE CAPLUS
L2	133	FILE EMBASE
L3	141	FILE MEDLINE
L4	251	FILE BIOSIS
L5	10	FILE USPATFULL
	TOTAL FOR ALL FILES	
L6	950	S CYTOCHROME P450 MONOOXYGENASE?
L7	0	FILE CAPLUS
L8	0	FILE EMBASE
L9	0	FILE MEDLINE
L10	0	FILE BIOSIS
L11	0	FILE USPATFULL
	TOTAL FOR ALL FILES	
L12	0	S L6 AND RITONAVIR
L13	74	FILE CAPLUS
L14	159	FILE EMBASE
L15	44	FILE MEDLINE
L16	96	FILE BIOSIS
L17	6	FILE USPATFULL
	TOTAL FOR ALL FILES	
L18	379	S L6 AND SAQUINAVIR OR VX-478 OR MK-639 OR AG1343 OR A-77
L19	29	FILE CAPLUS
L20	35	FILE EMBASE
L21	40	FILE MEDLINE
L22	31	FILE BIOSIS
L23	4	FILE USPATFULL
	TOTAL FOR ALL FILES	
L24	139	S L18 AND HIV PROTEASE INHIBITOR?
L25	0	FILE CAPLUS
L26	6	FILE EMBASE

L27	19	FILE MEDLINE
L28	3	FILE BIOSIS
L29	2	FILE USPATFULL
TOTAL FOR ALL FILES		
L30	30	S L24 AND METABOLI?

nelfinavir, indinavir and **VX-478**. Clinically significant drug interactions have been predicted between ritonavir and a range of medications. In patients with HIV-1 infection, ritonavir markedly reduced viral load within 2 weeks of treatment onset and also increased CD4+ cell counts. In a large placebo-controlled trial in patients with advanced HIV infection, the addition of ritonavir to existing therapy reduced the risk of mortality by 43% and clinical progression by 56% after 6.1 months. Triple therapy with ritonavir plus zidovudine, in combination with lamivudine or zalcitabine, reduced HIV viraemia to below detectable levels in most patients with acute, and some patients with advanced HIV infection in 2 small trials. Early results suggest combination therapy with ritonavir and saquinavir increases CD4+ cell counts and decreases HIV RNA levels in patients with previously untreated HIV infection.

CT Check Tags: Comparative Study; Human
Administration, Oral
*Anti-HIV Agents: PD, pharmacology
Anti-HIV Agents: PK, pharmacokinetics
Anti-HIV Agents: TU, therapeutic use
Biological Availability
Cytochrome P-450: GE, genetics
Cytochrome P-450: ME, metabolism
CD4-Positive T-Lymphocytes: CY, cytology
*CD4-Positive T-Lymphocytes: DE, drug effects
Dose-Response Relationship, Drug
Double-Blind Method
Drug Therapy, Combination
Drug Tolerance
*HIV Infections: DT, drug therapy
HIV Infections: GE, genetics
HIV Infections: MO, mortality
***HIV Protease Inhibitors: PD, pharmacology**
HIV Protease Inhibitors: PK, pharmacokinetics
HIV Protease Inhibitors: TU, therapeutic use
Lamivudine: AD, administration & dosage
Lamivudine: PD, pharmacology
Lamivudine: TU, therapeutic use
Leukocyte Count: DE, drug effects
Randomized Controlled Trials
Ritonavir: ME, metabolism
*Ritonavir: PD, pharmacology
Ritonavir: PK, pharmacokinetics
Ritonavir: TU, therapeutic use
RNA, Messenger: ME, metabolism
Zalcitabine: AD, administration & dosage
Zalcitabine: PD, pharmacology
Zalcitabine: TU, therapeutic use
Zidovudine: AD, administration & dosage
Zidovudine: PD, pharmacology
Zidovudine: TU, therapeutic use

CN 0 (Anti-HIV Agents); 0 (**HIV Protease Inhibitors**); 0 (Ritonavir); 0 (RNA, Messenger)

L30 ANSWER 13 OF 30 MEDLINE
ACCESSION NUMBER: 96431786 MEDLINE
TITLE: Antiviral and resistance studies of **AG1343**, an orally bioavailable inhibitor of human

immunodeficiency virus protease.

AUTHOR: Patick A K; Mo H; Markowitz M; Appelt K; Wu B; Musick L; Kalish V; Kaldor S; Reich S; Ho D; Webber S

CORPORATE SOURCE: Department of Pharmacology, Agouron Pharmaceuticals, Inc., San Diego, CA 92121, USA.

SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1996 Feb) 40 (2) 292-7.
Journal code: 6HK. ISSN: 0066-4804.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 9702

ENTRY WEEK: 19970204

AB **AG1343** ([3S-(3R*,4aR*,8aR*,2'S*,3'S*)]-2-[2' hydroxy-3'-phenylthiomethyl-4'-aza-5'-oxo-5'-(2''-methyl-3''-hydro xy-phenyl) pentyl]-decahydroiso-quinoline-3-N-t-butylcarboxamide methanesulfonic acid) is a selective, nonpeptidic inhibitor of human immunodeficiency virus (HIV) protease (Ki = 2 nM) that was discovered by protein structure-based drug design methodologies. **AG1343** was effective against the replication of several laboratory and clinical HIV type 1 (HIV-1) or HIV-2 isolates including pyridinone- and zidovudine-resistant strains, with 50% effective concentrations ranging from 9 to 60 nM. In reversibility studies, inhibition of gag (p55) proteolytic processing in HIV-1 particles from cells treated with **AG1343** was maintained for up to 36 h after drug removal. The ability of virus to develop resistance to **AG1343** was studied by serial passage of HIV-1 NL4.3 in the presence of increasing concentrations of drug. After 28 passages, a variant with a 30-fold reduction in susceptibility to **AG1343** was isolated. Molecular analysis of the protease from this variant indicated a double change from a Met to Ile at residue 46 and an Ile to Val or Ala at residue 84 (M46I+I84V, A). Consistent with these findings, reductions in susceptibility were observed for recombinant viruses constructed to contain the single I84V change or the double M46I+I84V substitutions. Resistance, however, was not detected for recombinant viruses containing other key mutations in HIV-1 protease, including a Val to Ile change at residue 32 or a Val to Ala or Phe at residue 82. The potent anti-HIV activity of **AG1343** against several isolates suggests that **AG1343** should perform well during ongoing human phase II clinical trials.

TI Antiviral and resistance studies of **AG1343**, an orally bioavailable inhibitor of human immunodeficiency virus protease.

AB **AG1343** ([3S-(3R*,4aR*,8aR*,2'S*,3'S*)]-2-[2' hydroxy-3'-phenylthiomethyl-4'-aza-5'-oxo-5'-(2''-methyl-3''-hydro xy-phenyl) pentyl]-decahydroiso-quinoline-3-N-t-butylcarboxamide methanesulfonic acid) is a selective, nonpeptidic inhibitor of human immunodeficiency virus (HIV) protease (Ki = 2 nM) that was discovered by protein structure-based drug design methodologies. **AG1343** was effective against the replication of several laboratory and clinical HIV type 1 (HIV-1) or HIV-2 isolates including pyridinone- and zidovudine-resistant strains, with 50% effective concentrations ranging from 9 to 60 nM. In reversibility studies, inhibition of gag (p55) proteolytic processing in HIV-1 particles from cells treated with **AG1343** was maintained for up to 36 h after drug removal. The ability of virus to develop resistance to **AG1343** was studied by serial passage of

HIV-1 NL4.3 in the presence of increasing concentrations of drug. After 28 passages, a variant with a 30-fold reduction in susceptibility to **AG1343** was isolated. Molecular analysis of the protease from this variant indicated a double change from a Met to Ile at residue 46 and an Ile to Val or Ala at residue 84 (M46I+I84V, A). Consistent with these findings, reductions in susceptibility were observed for recombinant viruses constructed to contain the single I84V change or the double M46I+I84V substitutions. Resistance, however, was not detected for recombinant viruses containing other key mutations in HIV-1 protease, including a Val to Ile change at residue 32 or a Val to Ala or Phe at residue 82. The potent anti-HIV activity of **AG1343** against several isolates suggests that **AG1343** should perform well during ongoing human phase II clinical trials.

CT Check Tags: Comparative Study
Amino Acid Sequence
*Antiviral Agents: PD, pharmacology
Cells, Cultured
Drug Resistance, Microbial
Gene Products, gag: ME, metabolism
***HIV Protease Inhibitors: PD, pharmacology**
*HIV-1: DE, drug effects
HIV-1: EN, enzymology
HIV-1: GE, genetics
*HIV-2: DE, drug effects
*Isoquinolines: PD, pharmacology
Microbial Sensitivity Tests
Molecular Sequence Data
Reverse Transcriptase Inhibitors: PD, pharmacology
Saquinavir: PD, pharmacology
*Sulfonic Acids: PD, pharmacology
Zidovudine: PD, pharmacology

CN 0 (Antiviral Agents); 0 (AG 1343); 0 (Gene Products, gag); 0 (**HIV Protease Inhibitors**); 0 (Isoquinolines); 0 (Reverse Transcriptase Inhibitors); 0 (Sulfonic Acids)

L30 ANSWER 14 OF 30 MEDLINE
ACCESSION NUMBER: 96417630 MEDLINE
TITLE: Role of cytochrome P450 3A4 in human **metabolism** of **MK-639**, a potent human immunodeficiency virus protease inhibitor.
AUTHOR: Chiba M; Hensleigh M; Nishime J A; Balani S K; Lin J H
CORPORATE SOURCE: Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA.
SOURCE: DRUG METABOLISM AND DISPOSITION, (1996 Mar) 24 (3) 307-14.
Journal code: EBR. ISSN: 0090-9556.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 9702
ENTRY WEEK: 19970204

AB **MK-639** (L-735,524) is a potent human immunodeficiency virus protease inhibitor under investigation in the

treatment of acquired immunodeficiency syndrome. Five in vitro approaches have been used to identify the cytochrome P450 isoform(s) responsible for the human microsomal oxidative **metabolism** of **MK-639**. These approaches are: 1) chemical inhibition; 2) immunochemical inhibition; 3) **metabolism** by cDNA-expressed human cytochrome P450 enzymes; 4) a correlation analysis; and 5) competitive inhibition of marker activities. Ketoconazole and troleandomycin, both selective inhibitors for cytochrome P450 3A4 (CYP3A4), markedly inhibited the formation of all oxidative **metabolites** of **MK-639**; whereas other inhibitors (furafylline, sulfaphenazole, quinidine, S-mephenytoin, and diethyldithiocarbamate) had little effect on **MK-639 metabolism**. This suggested the involvement of CYP3A4 in **MK-639 metabolism**. Consistent with this, an anti-rat CYP3A1 rabbit polyclonal antibody, which shows a cross-reactive inhibition of CYP3A4-dependent testosterone 6beta-hydroxylation in human liver microsomes, completely inhibited **MK-639 metabolism**. Human recombinant CYP3A4 showed a high **metabolic** activity to form all **MK-639 metabolites** found in native human liver microsomes. In addition, the formation of individual **MK-639 metabolites** correlated well with each other and with testosterone 6beta-hydroxylation in 12 different human liver microsomes, whereas no correlation was observed between **MK -639 metabolite** formation and bufuralol 1'-hydroxylation (or tolbutamide methyl hydroxylation). Furthermore, **MK-639** strongly inhibited testosterone 6beta-hydroxylation in a concentration-dependent manner. Kinetic analysis showed that **MK-639** is a very potent competitive inhibitor for testosterone 6beta-hydroxylation, with a Ki value of approximately 0.5 mu M. Collectively, these results consistently indicate that CYP3A4 is the isoform responsible for the oxidative **metabolism** of **MK-639** in human liver microsomes.

TI Role of cytochrome P450 3A4 in human **metabolism** of **MK-639**, a potent human immunodeficiency virus protease inhibitor.

AB **MK-639** (L-735,524) is a potent human immunodeficiency virus protease inhibitor under investigation in the treatment of acquired immunodeficiency syndrome. Five in vitro approaches have been used to identify the cytochrome P450 isoform(s) responsible for the human microsomal oxidative **metabolism** of **MK-639**. These approaches are: 1) chemical inhibition; 2) immunochemical inhibition; 3) **metabolism** by cDNA-expressed human cytochrome P450 enzymes; 4) a correlation analysis; and 5) competitive inhibition of marker activities. Ketoconazole and troleandomycin, both selective inhibitors for cytochrome P450 3A4 (CYP3A4), markedly inhibited the formation of all oxidative **metabolites** of **MK-639**; whereas other inhibitors (furafylline, sulfaphenazole, quinidine, S-mephenytoin, and diethyldithiocarbamate) had little effect on **MK-639 metabolism**. This suggested the involvement of CYP3A4 in **MK-639 metabolism**. Consistent with this, an anti-rat CYP3A1 rabbit polyclonal antibody, which shows a cross-reactive inhibition of CYP3A4-dependent testosterone 6beta-hydroxylation in human liver microsomes, completely inhibited **MK-639**

metabolism. Human recombinant CYP3A4 showed a high **metabolic** activity to form all **MK-639 metabolites** found in native human liver microsomes. In addition, the formation of individual **MK-639 metabolites** correlated well with each other and with testosterone 6beta-hydroxylation in 12 different human liver microsomes, whereas no correlation was observed between **MK -639 metabolite** formation and bufuralol 1'-hydroxylation (or tolbutamide methyl hydroxylation). Furthermore, **MK-639** strongly inhibited testosterone 6beta-hydroxylation in a concentration-dependent manner. Kinetic analysis showed that **MK-639** is a very potent competitive inhibitor for testosterone 6beta-hydroxylation, with a Ki value of approximately 0.5 mu M. Collectively, these results consistently indicate that CYP3A4 is the isoform responsible for the oxidative **metabolism** of **MK-639** in human liver microsomes.

CT Check Tags: Human
Antibiotics, Macrolide: PD, pharmacology
Antifungal Agents: PD, pharmacology
***Cytochrome P-450: ME, metabolism**
***Hydroxylases: ME, metabolism**
Hydroxylation: DE, drug effects
***HIV Protease Inhibitors: ME, metabolism**
***Indinavir: ME, metabolism**
Isoenzymes
Ketoconazole: PD, pharmacology
***Microsomes, Liver: ME, metabolism**
Troleandomycin: PD, pharmacology

CN EC 1.14. (Hydroxylases); EC 1.14.99.- (nifedipine oxidase); 0 (Antibiotics, Macrolide); 0 (Antifungal Agents); 0 (**HIV Protease Inhibitors**); 0 (Isoenzymes)

L30 ANSWER 15 OF 30 MEDLINE

ACCESSION NUMBER: 96338373 MEDLINE

TITLE: Human serum alpha 1 acid glycoprotein reduces uptake, intracellular concentration, and antiviral activity of **A-80987**, an inhibitor of the human immunodeficiency virus type 1 protease.

AUTHOR: Bilello J A; Bilello P A; Stellrecht K; Leonard J; Norbeck D W; Kempf D J; Robins T; Drusano G L

CORPORATE SOURCE: Department of Medicine, Albany Medical College, New York 12208, USA.

SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1996 Jun) 40 (6) 1491-7.
Journal code: 6HK. ISSN: 0066-4804.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 9704

ENTRY WEEK: 19970401

AB The therapeutic utility of a human immunodeficiency virus type 1 (HIV-1) protease inhibitor may depend on its intracellular concentration, which is a property of its uptake, **metabolism** , and/or efflux. Previous studies in our laboratory indicated that the addition of alpha 1 acid glycoprotein (alpha 1 AGP) to the medium markedly increased the amount of the drug required to limit

infection in vitro. In this study, physiologically relevant concentrations of alpha 1 AGP and a radiolabeled inhibitor, **A-80987**, were used to determine both the uptake and activity of the agent in HIV-1-infected human peripheral blood mononuclear cells and cell lines. Both the uptake and efflux of 14C-labeled **A-80987** were rapid (t1/2, < 5 min). Uptake of the drug was linearly dependent on the concentration but insensitive to the **metabolic** inhibitors KF, sodium cyanide, or CCCP (carbonyl cyanide m-chlorophenyl hydrazone). The amount of **A-80987** which entered the cells was inversely proportional to the concentration of alpha 1 AGP (r2, 0.99) and directly proportional to the amount of extracellular non-protein-bound drug (r2, 0.99). Most importantly, the antiviral activity of the drug in HIV-1-infected peripheral blood mononuclear cells and MT-2 cells was directly related to the amount of intracellular **A-80987**. This study demonstrates that **A-80987** binds to alpha 1 AGP, resulting in a free fraction below 10%. Cellular uptake of **A-80987** is proportionally decreased in the presence of alpha 1 AGP, which results in less-than-expected antiviral activity. Importantly, we demonstrate for the first time that the inhibition of HIV protease is highly correlated with the amount of intracellular inhibitor.

TI Human serum alpha 1 acid glycoprotein reduces uptake, intracellular concentration, and antiviral activity of **A-80987** , an inhibitor of the human immunodeficiency virus type 1 protease.

AB The therapeutic utility of a human immunodeficiency virus type 1 (HIV-1) protease inhibitor may depend on its intracellular concentration, which is a property of its uptake, **metabolism** , and/or efflux. Previous studies in our laboratory indicated that the addition of alpha 1 acid glycoprotein (alpha 1 AGP) to the medium markedly increased the amount of the drug required to limit infection in vitro. In this study, physiologically relevant concentrations of alpha 1 AGP and a radiolabeled inhibitor, **A-80987**, were used to determine both the uptake and activity of the agent in HIV-1-infected human peripheral blood mononuclear cells and cell lines. Both the uptake and efflux of 14C-labeled **A-80987** were rapid (t1/2, < 5 min). Uptake of the drug was linearly dependent on the concentration but insensitive to the **metabolic** inhibitors KF, sodium cyanide, or CCCP (carbonyl cyanide m-chlorophenyl hydrazone). The amount of **A-80987** which entered the cells was inversely proportional to the concentration of alpha 1 AGP (r2, 0.99) and directly proportional to the amount of extracellular non-protein-bound drug (r2, 0.99). Most importantly, the antiviral activity of the drug in HIV-1-infected peripheral blood mononuclear cells and MT-2 cells was directly related to the amount of intracellular **A-80987**. This study demonstrates that **A-80987** binds to alpha 1 AGP, resulting in a free fraction below 10%. Cellular uptake of **A-80987** is proportionally decreased in the presence of alpha 1 AGP, which results in less-than-expected antiviral activity. Importantly, we demonstrate for the first time that the inhibition of HIV protease is highly correlated with the amount of intracellular inhibitor.

CT Check Tags: Human
Cell Line
HIV Protease Inhibitors: ME, metabolism

***HIV Protease Inhibitors: PK, pharmacokinetics**
*HIV-1: DE, drug effects
HIV-1: ME, metabolism
Orosomucoid: ME, metabolism
*Orosomucoid: PD, pharmacology
Polymerase Chain Reaction
Protein Binding
Pyridines: ME, metabolism
*Pyridines: PK, pharmacokinetics
RNA, Viral: DE, drug effects
CN 0 (**A 80987**); 0 (**HIV Protease Inhibitors**); 0 (Orosomucoid); 0 (Pyridines); 0 (RNA, Viral)

L30 ANSWER 16 OF 30 MEDLINE
ACCESSION NUMBER: 96298219 MEDLINE
TITLE: In vitro **metabolism** of a potent **HIV -protease inhibitor** (141W94) using rat, monkey and human liver S9.
AUTHOR: Singh R; Chang S Y; Taylor L C
CORPORATE SOURCE: Glaxo Wellcome Inc., Research Triangle Park, NC 27709, USA.
SOURCE: RAPID COMMUNICATIONS IN MASS SPECTROMETRY, (1996) 10 (9) 1019-26.
Journal code: A9Q. ISSN: 0951-4198.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 9704
ENTRY WEEK: 19970403
AB Compound 141W94 (Vertex VX478) (3S)-tetrahydro-3-furyl N-[((S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl] carbamate, is a potent **HIV-protease inhibitor** and is currently undergoing clinical trials. The purpose of this study was the rapid identification of the phase I and II in vitro **metabolite** of 141W94 using mass spectrometry. Four different sources of liver S9 fractions were used for studying comparative in vitro **metabolism** of 141W94. They were obtained from Arochlor-induced rat, normal (untreated) rat, cynomolgus monkey and human livers. Selected incubations were supplemented with uridine diphosphate glucuronic acid and the reduced form of glutathione. The predominant species seen in the incubation mixture was the parent compound 141W94. **Metabolites** arising from ring opening to form the diol and carboxylic acid and oxidation of the tetrahydrofurran ring (formation of dihydrofuran) were identified. In addition, of the two monohydroxylated products identified, one resulted from hydroxylation on the aniline ring and the other from hydroxylation at the benzylic position. Two different glucuronides were also observed. Comparing the three species, very little **metabolism** was seen in the normal (non-induced) rat. The **metabolic** profile and extent of **metabolism** with induced rat, monkey and human S9 was similar. Induced rat S9 incubation showed the formation of two unique **metabolites** that were not seen in non-induced rat, monkey and human S9 fractions. They were the monohydroxylated glucuronide and a carbamate cleavage product. The **metabolites** were identified using mass spectrometry based on their molecular masses

and fragmentation patterns.

TI In vitro **metabolism** of a potent **HIV-protease inhibitor** (141W94) using rat, monkey and human liver S9.

AB Compound 141W94 (Vertex VX478) (3S)-tetrahydro-3-furyl N-[((S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl] carbamate, is a potent **HIV-protease inhibitor** and is currently undergoing clinical trials. The purpose of this study was the rapid identification of the phase I and II in vitro **metabolite** of 141W94 using mass spectrometry. Four different sources of liver S9 fractions were used for studying comparative in vitro **metabolism** of 141W94. They were obtained from Arochlor-induced rat, normal (untreated) rat, cynomolgus monkey and human livers. Selected incubations were supplemented with uridine diphosphate glucuronic acid and the reduced form of glutathione. The predominant species seen in the incubation mixture was the parent compound 141W94. **Metabolites** arising from ring opening to form the diol and carboxylic acid and oxidation of the tetrahydrofurran ring (formation of dihydrofuran) were identified. In addition, of the two monohydroxylated products identified, one resulted from hydroxylation on the aniline ring and the other from hydroxylation at the benzylic position. Two different glucuronides were also observed. Comparing the three species, very little **metabolism** was seen in the normal (non-induced) rat. The **metabolic** profile and extent of **metabolism** with induced rat, monkey and human S9 was similar. Induced rat S9 incubation showed the formation of two unique **metabolites** that were not seen in non-induced rat, monkey and human S9 fractions. They were the monohydroxylated glucuronide and a carbamate cleavage product. The **metabolites** were identified using mass spectrometry based on their molecular masses and fragmentation patterns.

CT Check Tags: Animal; Comparative Study; Human; In Vitro
Aroclors: PD, pharmacology
Chromatography, High Pressure Liquid
***HIV Protease Inhibitors: ME, metabolism**
Liver: CY, cytology
***Liver: ME, metabolism**
Macaca fascicularis
Rats
Rats, Sprague-Dawley
Species Specificity
Spectrophotometry, Ultraviolet
Spectrum Analysis, Mass
Subcellular Fractions: ME, metabolism
***Sulfonamides: ME, metabolism**

CN 0 (Aroclors); 0 (**HIV Protease Inhibitors**); 0 (Sulfonamides); 0 (**VX 478**)

L30 ANSWER 17 OF 30 MEDLINE
ACCESSION NUMBER: 96279343 MEDLINE
TITLE: Kinetic characterization of human immunodeficiency virus type-1 protease-resistant variants.
AUTHOR: Pazhanisamy S; Stuver C M; Cullinan A B; Margolin N; Rao B G; Livingston D J
CORPORATE SOURCE: Vertex Pharmaceuticals Incorporated, Cambridge, Massachusetts 02139, USA.

08687774

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Jul 26) 271 (30) 17979-85.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 9611

AB Passage of human immunodeficiency virus type-1 (HIV-1) in T-lymphocyte cell lines in the presence of increasing concentrations of the hydroxylethylamino sulfonamide inhibitor **VX-478** or VB-11328 results in sequential accumulation of mutations in HIV-1 protease. We have characterized recombinant HIV-1 proteases that contain these mutations either individually (L10F, M46I, I47V, I50V) or in combination (the double mutant L10F/I50V and the triple mutant M46I/I47V/I50V). The catalytic properties and affinities for sulfonamide inhibitors and other classes of inhibitors were determined. For the I50V mutant, the efficiency (kcat/Km) of processing peptides designed to mimic cleavage junctions in the HIV-1 gag-pol polypeptide was decreased up to 25-fold. The triple mutant had a 2-fold higher processing efficiency than the I50V single mutant for peptide substrates with Phe/Pro and Tyr/Pro cleavage sites, suggesting that the M46I and I47V mutations are compensatory. The effects of mutation on processing efficiency were used in conjunction with the inhibition constant (Ki) to evaluate the advantage of the mutation for viral replication in the presence of drug. These analyses support the virological observation that the addition of M46I and I47V mutations on the I50V mutant background enables increased survival of the HIV-1 virus as it replicates in the presence of **VX-478**. Crystal structures and molecular models of the active site of the HIV-1 protease mutants suggest that changes in the active site can selectively affect the binding energy of inhibitors with little corresponding change in substrate binding.

AB Passage of human immunodeficiency virus type-1 (HIV-1) in T-lymphocyte cell lines in the presence of increasing concentrations of the hydroxylethylamino sulfonamide inhibitor **VX-478** or VB-11328 results in sequential accumulation of mutations in HIV-1 protease. We have characterized recombinant HIV-1 proteases that contain these mutations either individually (L10F, M46I, I47V, I50V) or in combination (the double mutant L10F/I50V and the triple mutant M46I/I47V/I50V). The catalytic properties and affinities for sulfonamide inhibitors and other classes of inhibitors were determined. For the I50V mutant, the efficiency (kcat/Km) of processing peptides designed to mimic cleavage junctions in the HIV-1 gag-pol polypeptide was decreased up to 25-fold. The triple mutant had a 2-fold higher processing efficiency than the I50V single mutant for peptide substrates with Phe/Pro and Tyr/Pro cleavage sites, suggesting that the M46I and I47V mutations are compensatory. The effects of mutation on processing efficiency were used in conjunction with the inhibition constant (Ki) to evaluate the advantage of the mutation for viral replication in the presence of drug. These analyses support the virological observation that the addition of M46I and I47V mutations on the I50V mutant background enables increased survival of the HIV-1 virus as it replicates in the presence of **VX-478**. Crystal structures and molecular models of the active site of the HIV-1 protease mutants suggest that changes in the active site can

selectively affect the binding energy of inhibitors with little corresponding change in substrate binding.

CT Check Tags: Comparative Study
Amino Acid Sequence
Binding Sites
Hydrolysis
HIV Protease: DE, drug effects
*HIV Protease: GE, genetics
HIV Protease Inhibitors: PD, pharmacology
*HIV-1: EN, enzymology
*HIV-1: GE, genetics
Isoquinolines: PD, pharmacology
Kinetics
Models, Molecular
Molecular Sequence Data
*Mutation
Oligopeptides: ME, metabolism
Pyridines: PD, pharmacology
Quinolines: PD, pharmacology
Selection (Genetics)
Substrate Specificity
Sulfonamides: PD, pharmacology
Variation (Genetics)

CN EC 3.4.23.- (HIV Protease); 0 (**HIV Protease Inhibitors**); 0 (Isoquinolines); 0 (Oligopeptides); 0 (Pyridines); 0 (Quinolines); 0 (Sulfonamides); 0 (**VX 478**)

L30 ANSWER 18 OF 30 MEDLINE
ACCESSION NUMBER: 96217762 MEDLINE
TITLE: Relevance of plasma protein binding to antiviral activity and clinical efficacy of inhibitors of human immunodeficiency virus protease [letter; comment].
COMMENT: Comment on: J Infect Dis 1995 Nov;172(5):1238-45
AUTHOR: Bilello J A; Drusano G L
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1996 Jun) 173 (6) 1524-6.
Journal code: IH3. ISSN: 0022-1899.
PUB. COUNTRY: United States
Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 9609

CT Check Tags: Human
Antiviral Agents: ME, metabolism
*Antiviral Agents: PD, pharmacology
***Blood Proteins: ME, metabolism**
Clinical Trials
*HIV: DE, drug effects
HIV Infections: DT, drug therapy
HIV Protease Inhibitors: ME, metabolism
***HIV Protease Inhibitors: PD, pharmacology**
Orosomucoid: ME, metabolism
Protein Binding
Sulfonamides: ME, metabolism
*Sulfonamides: PD, pharmacology

CN 0 (Antiviral Agents); 0 (Blood Proteins); 0 (**HIV**

Protease Inhibitors); 0 (Orosomucoid); 0 (Sulfonamides); 0 (**VX 478**)

L30 ANSWER 19 OF 30 MEDLINE
ACCESSION NUMBER: 96202332 MEDLINE
TITLE: Human immunodeficiency virus type 1 viral background plays a major role in development of resistance to protease inhibitors.
AUTHOR: Rose R E; Gong Y F; Greytok J A; Bechtold C M; Terry B J; Robinson B S; Alam M; Colonno R J; Lin P F
CORPORATE SOURCE: Department of Virology, Bristol-Myers Squibb Company, Wallingford, CT 06492, USA.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Feb 20) 93 (4) 1648-53.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 9609

AB The observed in vitro and in vivo benefit of combination treatment with anti-human immunodeficiency virus (HIV) agents prompted us to examine the potential of resistance development when two protease inhibitors are used concurrently. Recombinant HIV-1 (NL4-3) proteases containing combined resistance mutations associated with BMS-186318 and **A-77003** (or saquinavir) were
either inactive or had impaired enzyme activity. Subsequent construction of HIV-1 (NL4-3) proviral clones containing the same mutations yielded viruses that were severely impaired in growth or nonviable, confirming that combination therapy may be advantageous. However, passage of BMS-186318-resistant HIV-1 (RF) in the presence of either saquinavir or SC52151, which represented sequential drug treatment, produced viable viruses resistant to both BMS-186318 and the second compound. The predominant breakthrough virus contained the G48V/A71T/V82A protease mutations. The clone-purified RF (G48V/A71T/V82A) virus, unlike the corresponding defective NL4-3 triple mutant, grew well and displayed cross-resistance to four distinct protease inhibitors. Chimeric virus and in vitro mutagenesis studies indicated that the RF-specific protease sequence, specifically the Ile at residue 10, enabled the NL4-3 strain with the triple mutant to grow. Our results clearly indicate that viral genetic background will play a key role in determining whether cross-resistance variants will arise.

AB The observed in vitro and in vivo benefit of combination treatment with anti-human immunodeficiency virus (HIV) agents prompted us to examine the potential of resistance development when two protease inhibitors are used concurrently. Recombinant HIV-1 (NL4-3) proteases containing combined resistance mutations associated with BMS-186318 and **A-77003** (or saquinavir) were
either inactive or had impaired enzyme activity. Subsequent construction of HIV-1 (NL4-3) proviral clones containing the same mutations yielded viruses that were severely impaired in growth or nonviable, confirming that combination therapy may be advantageous. However, passage of BMS-186318-resistant HIV-1 (RF) in the presence of either saquinavir or SC52151, which represented sequential drug treatment, produced viable viruses resistant to both BMS-186318 and the second compound. The predominant breakthrough virus contained

the G48V/A71T/V82A protease mutations. The clone-purified RF (G48V/A71T/V82A) virus, unlike the corresponding defective NL4-3 triple mutant, grew well and displayed cross-resistance to four distinct protease inhibitors. Chimeric virus and in vitro mutagenesis studies indicated that the RF-specific protease sequence, specifically the Ile at residue 10, enabled the NL4-3 strain with the triple mutant to grow. Our results clearly indicate that viral genetic background will play a key role in determining whether cross-resistance variants will arise.

CT Check Tags: Comparative Study; Human
Amino Acid Sequence
Carbamates: PD, pharmacology
Clone Cells
Drug Administration Schedule
Drug Resistance, Microbial: GE, genetics
Drug Therapy, Combination
DNA Mutational Analysis
DNA, Recombinant: GE, genetics
DNA, Viral: GE, genetics
Ethanolamines: PD, pharmacology
Hela Cells
*HIV Protease: GE, genetics
HIV Protease Inhibitors: AD, administration & dosage
***HIV Protease Inhibitors: PD, pharmacology**
*HIV-1: DE, drug effects
HIV-1: EN, enzymology
HIV-1: GE, genetics
Isoquinolines: PD, pharmacology
Methylurea Compounds: PD, pharmacology
Molecular Sequence Data
Point Mutation
Proviruses: EN, enzymology
Proviruses: GE, genetics
Pyridines: PD, pharmacology
Quinolines: PD, pharmacology
Recombinant Fusion Proteins: AI, antagonists & inhibitors
Recombinant Fusion Proteins: ME, metabolism
T-Lymphocytes
Urea: AA, analogs & derivatives
Urea: PD, pharmacology

CN EC 3.4.23.- (HIV Protease); 0 (BMS 186318); 0 (Carbamates); 0 (DNA, Recombinant); 0 (DNA, Viral); 0 (Ethanolamines); 0 (**HIV Protease Inhibitors**); 0 (Isoquinolines); 0 (Methylurea Compounds); 0 (Pyridines); 0 (Quinolines); 0 (Recombinant Fusion Proteins); 0 (SC 52151)

L30 ANSWER 20 OF 30 MEDLINE
ACCESSION NUMBER: 96139551 MEDLINE
TITLE: Efficacy of constant infusion of **A-77003**, an inhibitor of the human immunodeficiency virus type 1 (HIV-1) protease, in limiting acute HIV-1 infection in vitro.
AUTHOR: Bilello J A; Bilello P A; Kort J J; Dudley M N; Leonard J; Drusano G L
CORPORATE SOURCE: Department of Medicine, Albany Medical College, New York 12208, USA.
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1995 Nov) 39 (11) 2523-7.

Journal code: 6HK. ISSN: 0066-4804.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 9605

AB **A-77003**, a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, is effective for both acute and chronic infection in vitro and was evaluated clinically by continuous intravenous infusion administration. The minimum effective dose (the concentration required to completely inhibit viral replication) was determined in vitro in a population of uninfected (99%) and HIV-infected (1%) cells exposed to **A-77003** by continuous infusion in hollow-fiber bioreactors. The production of infectious HIV and release of p24 antigen from infected cells were completely inhibited in cultures exposed to **A-77003** at or above a concentration of 0.5 microM. Measurement of unintegrated HIV-1 DNA synthesis and flow cytometric analysis for cells expressing HIV p24 antigen demonstrated that the spread of HIV to uninfected cells was also blocked at 0.5 microM **A-77003**. Dose deescalation to 0.25 microM or removal of **A-77003** resulted in the limited spread of the virus throughout the culture, the resumption of viral DNA synthesis, and release of p24. HIV produced after exposure to 0.5 microM **A-77003** was noninfectious for a period of 72 h after the removal of the drug. Addition of 1 mg of alpha 1-acid glycoprotein per ml to this in vitro system completely ablated the anti-HIV effect of 0.5 microM **A-77003**. These data suggest that determination of the minimum effective dose under conditions which simulate human pharmacodynamic patterns may be useful in determining the initial dose and schedule for clinical trials. However, other factors, such as serum protein binding, may influence the selection of a therapeutic regimen.

TI Efficacy of constant infusion of **A-77003**, an inhibitor of the human immunodeficiency virus type 1 (HIV-1) protease, in limiting acute HIV-1 infection in vitro.

AB **A-77003**, a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, is effective for both acute and chronic infection in vitro and was evaluated clinically by continuous intravenous infusion administration. The minimum effective dose (the concentration required to completely inhibit viral replication) was determined in vitro in a population of uninfected (99%) and HIV-infected (1%) cells exposed to **A-77003** by continuous infusion in hollow-fiber bioreactors. The production of infectious HIV and release of p24 antigen from infected cells were completely inhibited in cultures exposed to **A-77003** at or above a concentration of 0.5 microM. Measurement of unintegrated HIV-1 DNA synthesis and flow cytometric analysis for cells expressing HIV p24 antigen demonstrated that the spread of HIV to uninfected cells was also blocked at 0.5 microM **A-77003**. Dose deescalation to 0.25 microM or removal of **A-77003** resulted in the limited spread of the virus throughout the culture, the resumption of viral DNA synthesis, and release of p24. HIV produced after exposure to 0.5 microM **A-77003** was noninfectious for a period of 72 h after the removal of the drug. Addition of 1 mg of alpha 1-acid glycoprotein per ml to this in vitro system completely ablated the anti-HIV effect of 0.5 microM **A-77003**. These

data suggest that determination of the minimum effective dose under conditions which simulate human pharmacodynamic patterns may be useful in determining the initial dose and schedule for clinical trials. However, other factors, such as serum protein binding, may influence the selection of a therapeutic regimen.

CT Check Tags: Human
Antiviral Agents: AD, administration & dosage
*Antiviral Agents: PD, pharmacology
Cell Line
Dose-Response Relationship, Drug
DNA, Viral: BI, biosynthesis
Flow Cytometry
HIV Core Protein p24: ME, metabolism
HIV Protease Inhibitors: AD, administration & dosage
***HIV Protease Inhibitors: PD, pharmacology**
*HIV-1: DE, drug effects
HIV-1: PH, physiology
Methylurea Compounds: AD, administration & dosage
*Methylurea Compounds: PD, pharmacology
Orosomucoid: ME, metabolism
Orosomucoid: PD, pharmacology
Polymerase Chain Reaction
Pyridines: AD, administration & dosage
*Pyridines: PD, pharmacology
T-Lymphocytes: VI, virology
Virus Replication: DE, drug effects

CN 0 (Antiviral Agents); 0 (DNA, Viral); 0 (HIV Core Protein p24); 0 (**HIV Protease Inhibitors**); 0 (Methylurea Compounds); 0 (Orosomucoid); 0 (Pyridines)

L30 ANSWER 21 OF 30 MEDLINE
ACCESSION NUMBER: 96036379 MEDLINE
TITLE: Weak binding of **VX-478** to human plasma proteins and implications for anti-human immunodeficiency virus therapy [see comments].
COMMENT: Comment in: J Infect Dis 1996 Jun;173(6):1524-6
AUTHOR: Livington D J; Pazhanisamy S; Porter D J; Partaledis J A; Tung R D; Painter G R
CORPORATE SOURCE: Vertex Pharmaceuticals Inc., Cambridge, MA 02139, USA.
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1995 Nov) 172 (5) 1238-45.
Journal code: IH3. ISSN: 0022-1899.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 9602

AB **VX-478** is a potent inhibitor of human immunodeficiency virus type 1 (HIV-1) protease (Ki, 0.6 nM) and of HIV-1 replication in antiviral assays (IC90, 80 nM). The fractional binding of **VX-478** to human plasma and to purified plasma proteins was determined by equilibrium dialysis and difference UV spectrophotometry. Binding to alpha 1-acid glycoprotein (89% at 2 microM total drug concentration, Kd of 4 microM) accounts for its fractional binding in plasma (93%). Stopped-flow spectrophotometry methods showed that binding is a reversible two-step process. The measured dissociation rate constant

approaches 100 s-1. The antiviral effect of **VX-478** was determined in the presence of 45% human plasma, in which the IC90 increased by 1.5-fold compared with control experiments in the presence of 15% fetal bovine serum. The effects of protein binding on the antiviral activity of **VX-478** are minor, as expected for a weak drug-protein interaction.

TI Weak binding of **VX-478** to human plasma proteins and implications for anti-human immunodeficiency virus therapy [see comments].

AB **VX-478** is a potent inhibitor of human immunodeficiency virus type 1 (HIV-1) protease (Ki, 0.6 nM) and of HIV-1 replication in antiviral assays (IC90, 80 nM). The fractional binding of **VX-478** to human plasma and to purified plasma proteins was determined by equilibrium dialysis and difference UV spectrophotometry. Binding to alpha 1-acid glycoprotein (89% at 2 microM total drug concentration, Kd of 4 microM) accounts for its fractional binding in plasma (93%). Stopped-flow spectrophotometry methods showed that binding is a reversible two-step process. The measured dissociation rate constant approaches 100 s-1. The antiviral effect of **VX-478** was determined in the presence of 45% human plasma, in which the IC90 increased by 1.5-fold compared with control experiments in the presence of 15% fetal bovine serum. The effects of protein binding on the antiviral activity of **VX-478** are minor, as expected for a weak drug-protein interaction.

CT Check Tags: Animal; Human
*Acquired Immunodeficiency Syndrome: DT, drug therapy
*Antiviral Agents: BL, blood
Blood
***Blood Proteins: ME, metabolism**
Cattle
Fetus
***HIV Protease Inhibitors: BL, blood**
Kinetics
Molecular Structure
***Orosomucoid: ME, metabolism**
Protein Binding
Spectrophotometry, Ultraviolet
*Sulfonamides: BL, blood

CN 0 (Antiviral Agents); 0 (Blood Proteins); 0 (**HIV Protease Inhibitors**); 0 (Orosomucoid); 0 (Sulfonamides); 0 (**VX 478**)

L30 ANSWER 22 OF 30 MEDLINE
ACCESSION NUMBER: 95363927 MEDLINE
TITLE: In vitro selection and characterization of human immunodeficiency virus type 1 (HIV-1) isolates with reduced sensitivity to hydroxyethylamino sulfonamide inhibitors of HIV-1 aspartyl protease.
AUTHOR: Partaledis J A; Yamaguchi K; Tisdale M; Blair E E; Falcione C; Maschera B; Myers R E; Pazhanisamy S; Futer O; Cullinan A B; et al
CORPORATE SOURCE: Vertex Pharmaceuticals Incorporated, Cambridge, Massachusetts 02139-4211, USA.
SOURCE: JOURNAL OF VIROLOGY, (1995 Sep) 69 (9) 5228-35. Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

08687774

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 9511

AB Human immunodeficiency virus type 1 (HIV-1) variants with reduced sensitivity to the hydroxyethylamino sulfonamide protease inhibitors VB-11,328 and **VX-478** have been selected in vitro by two independent serial passage protocols with HIV-1 in CEM-SS and MT-4 cell lines. Virus populations with greater than 100-fold-increased resistance to both inhibitors compared with the parental virus have been obtained. DNA sequence analyses of the protease genes from VB-11,328- and **VX-478** -resistant variants reveal a sequential accumulation of point mutations, with similar resistance patterns occurring for the two inhibitors. The deduced amino acid substitutions in the resistant protease are Leu-10-->Phe, Met-46-->Ile, Ile-47-->Val, and Ile-50-->Val. This is the first observation in HIV protease resistance studies of an Ile-50-->Val mutation, a mutation that appears to arise uniquely against the sulfonamide inhibitor class. When the substitutions observed were introduced as single mutations into an HIV-1 infectious clone (HXB2), only the Ile-50-->Val mutant showed reduced sensitivity (two- to threefold) to VB-11,328 and **VX-478**. A triple protease mutant infectious clone carrying the mutations Met-46-->Ile, Ile-47-->Val, and Ile-50-->Val, however, showed much greater reduction in sensitivity (14- to 20-fold) to VB-11,328 and **VX-478**. The same mutations were studied in recombinant HIV protease. The mutant protease Ile-50-->Val displays a much lower affinity for the inhibitors than the parent enzyme (< or = 80-fold). The protease triply mutated at Met-46-->Ile, Ile-47-->Val, and Ile-50-->Val shows an even greater decrease in inhibitor binding (< or = 270-fold). The sulfonamide-resistant HIV protease variants remain sensitive to inhibitors from other chemical classes (Ro 31-8959 and L-735,524), suggesting possibilities for clinical use of **HIV protease inhibitors** in combination or serially.

AB Human immunodeficiency virus type 1 (HIV-1) variants with reduced sensitivity to the hydroxyethylamino sulfonamide protease inhibitors VB-11,328 and **VX-478** have been selected in vitro by two independent serial passage protocols with HIV-1 in CEM-SS and MT-4 cell lines. Virus populations with greater than 100-fold-increased resistance to both inhibitors compared with the parental virus have been obtained. DNA sequence analyses of the protease genes from VB-11,328- and **VX-478** -resistant variants reveal a sequential accumulation of point mutations, with similar resistance patterns occurring for the two inhibitors. The deduced amino acid substitutions in the resistant protease are Leu-10-->Phe, Met-46-->Ile, Ile-47-->Val, and Ile-50-->Val. This is the first observation in HIV protease resistance studies of an Ile-50-->Val mutation, a mutation that appears to arise uniquely against the sulfonamide inhibitor class. When the substitutions observed were introduced as single mutations into an HIV-1 infectious clone (HXB2), only the Ile-50-->Val mutant showed reduced sensitivity (two- to threefold) to VB-11,328 and **VX-478**. A triple protease mutant infectious clone carrying the mutations Met-46-->Ile, Ile-47-->Val, and Ile-50-->Val, however, showed much greater reduction in sensitivity (14- to 20-fold) to VB-11,328 and **VX-478**. The same mutations were studied in recombinant HIV protease. The mutant protease Ile-50-->Val displays a much lower affinity for the

inhibitors than the parent enzyme (< or = 80-fold). The protease triply mutated at Met-46-->Ile, Ile-47-->Val, and Ile-50-->Val shows an even greater decrease in inhibitor binding (< or = 270-fold). The sulfonamide-resistant HIV protease variants remain sensitive to inhibitors from other chemical classes (Ro 31-8959 and L-735,524), suggesting possibilities for clinical use of **HIV protease inhibitors** in combination or serially.

CT Check Tags: Comparative Study; Human
Amino Acid Sequence
Base Sequence
Cell Line
DNA Primers
HIV Protease: CH, chemistry
***HIV Protease: ME, metabolism**
***HIV Protease Inhibitors: PD, pharmacology**
*HIV-1: DE, drug effects
HIV-1: IP, isolation & purification
HIV-1: PH, physiology
Kinetics
Microbial Sensitivity Tests
Models, Molecular
Molecular Sequence Data
Molecular Structure
Mutagenesis, Site-Directed
Point Mutation
Polymerase Chain Reaction
Protein Conformation
Recombinant Proteins: AI, antagonists & inhibitors
Recombinant Proteins: BI, biosynthesis
Recombinant Proteins: CH, chemistry
Structure-Activity Relationship
*Sulfonamides: PD, pharmacology
T-Lymphocytes
Virus Replication: DE, drug effects

CN EC 3.4.23.- (HIV Protease); 0 (DNA Primers); 0 (**HIV Protease Inhibitors**); 0 (Recombinant Proteins); 0 (Sulfonamides); 0 (VB 11328); 0 (**VX 478**)

L30 ANSWER 23 OF 30 MEDLINE
ACCESSION NUMBER: 95352609 MEDLINE
TITLE: Kinetic characterization and cross-resistance patterns of HIV-1 protease mutants selected under drug pressure.
AUTHOR: Gulnik S V; Suvorov L I; Liu B; Yu B; Anderson B; Mitsuya H; Erickson J W
CORPORATE SOURCE: SAIC-Frederick, National Cancer Institute-Frederick Cancer Research and Development Center, Maryland 21702-1201, USA.
SOURCE: BIOCHEMISTRY, (1995 Jul 25) 34 (29) 9282-7.
Journal code: A0G. ISSN: 0006-2960.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 9511

AB Eleven different recombinant, drug-resistant HIV-1 protease (HIV PR) mutants--R8Q, V32I, M46I, V82A, V82F, V82I, I84V, V32I/I84V, M46I/V82F, M46I/I84V, and V32I/K45I/F53L/A71V/I84V/L89M--were

generated on the basis of results of in vitro selection experiments using the inhibitors **A-77003**, A-84538, and KNI-272. Kinetic parameters of mutant and wild-type (WT) enzymes were measured along with inhibition constants (Ki) toward the inhibitors **A-77003**, A-84538, KNI-272, L-735,524, and Ro31-8959. The catalytic efficiency, kcat/Km, for the mutants decreased relative to WT by a factor of 1.2-14.8 and was mainly due to the elevation of Km. The effects of specific mutations on Ki values were unique with respect to both inhibitor and mutant enzyme. A new property, termed vitality, defined as the ratio (Kikcat/Km)mutant/(Kikcat/Km)WT was introduced to compare the selective advantage of different mutants in the presence of a given inhibitor. High vitality values were generally observed with mutations that emerged during in vitro selection studies. The kinetic model along with the panel of mutants described here should be useful for evaluating and predicting patterns of resistance for HIV PR inhibitors and may aid in the selection of inhibitor combinations to combat drug resistance.

AB Eleven different recombinant, drug-resistant HIV-1 protease (HIV PR) mutants--R8Q, V32I, M46I, V82A, V82F, V82I, I84V, V32I/I84V, M46I/V82F, M46I/I84V, and V32I/K45I/F53L/A71V/I84V/L89M--were generated on the basis of results of in vitro selection experiments using the inhibitors **A-77003**, A-84538, and KNI-272. Kinetic parameters of mutant and wild-type (WT) enzymes were measured along with inhibition constants (Ki) toward the inhibitors **A-77003**, A-84538, KNI-272, L-735,524, and Ro31-8959. The catalytic efficiency, kcat/Km, for the mutants decreased relative to WT by a factor of 1.2-14.8 and was mainly due to the elevation of Km. The effects of specific mutations on Ki values were unique with respect to both inhibitor and mutant enzyme. A new property, termed vitality, defined as the ratio (Kikcat/Km)mutant/(Kikcat/Km)WT was introduced to compare the selective advantage of different mutants in the presence of a given inhibitor. High vitality values were generally observed with mutations that emerged during in vitro selection studies. The kinetic model along with the panel of mutants described here should be useful for evaluating and predicting patterns of resistance for HIV PR inhibitors and may aid in the selection of inhibitor combinations to combat drug resistance.

CT Check Tags: Comparative Study
Amino Acid Sequence
Binding Sites
Carbamates: PD, pharmacology
Cloning, Molecular
Drug Resistance, Microbial
***HIV Protease: ME, metabolism**
***HIV Protease Inhibitors: PD, pharmacology**
*HIV-1: EN, enzymology
Isoquinolines: PD, pharmacology
Kinetics
Methylurea Compounds: PD, pharmacology
Mutagenesis, Site-Directed
Oligopeptides: PD, pharmacology
*Point Mutation
Pyridines: PD, pharmacology
Quinolines: PD, pharmacology
Recombinant Proteins: ME, metabolism
Structure-Activity Relationship

11/12/97

08687774

#4,12,

=> d ibib ab hit 1-

L30 ANSWER 1 OF 30 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97299931 EMBASE
TITLE: Human immunodeficiency virus protease inhibitors From drug design to clinical studies.
AUTHOR: Lin J.H.
CORPORATE SOURCE: J.H. Lin, Drug Metabolism, Mercke Research Laboratories, West Point, PA 19486, United States
SOURCE: Advanced Drug Delivery Reviews, (1997) 27/2-3 (215-233).
Refs: 58
ISSN: 0169-409X CODEN: ADDREP
PUBLISHER IDENT.: S 0169-409X(97)00044-6
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The discovery of human immunodeficiency virus (**HIV**) **protease inhibitors** is an example in which pharmacokinetic evaluation was implemented early in the discovery phase to obtain optimal pharmacological and pharmacokinetic properties. Currently, three **HIV protease inhibitors**, saquinavir, indinavir and ritonavir are clinically available. As a family, these **HIV protease inhibitors** are characterized pharmacologically by their ability to inhibit the viral protease enzyme. Pharmacokinetically, they are quite different due to their dissimilarity in physicochemical properties. Bioavailability appears to be limited with saquinavir, but not with indinavir and ritonavir. Although all three drugs are **metabolized** extensively by cytochrome P-450, saquinavir and indinavir are high clearance drugs while ritonavir is a low clearance drug. Despite their significant differences in elimination clearance, all three HIV proteases are given at high oral doses (600-800 mg) either twice or three times daily. These **HIV protease inhibitors** show superior therapeutic activity and a more favorable safety profile than those reported for the established reverse transcriptase inhibitors. However, the potential for interactions with other drugs **metabolized** by the CYP 3A4 isoform appears to be considerable. In addition, repeated administration of enzyme inducers results in a substantial decrease of plasma concentrations of protease inhibitors. Therefore, co-administration of drugs, such as rifampicin and rifabutin, must be avoided. **HIV protease inhibitors** are promising in the treatment of AIDS. Although they are not a cure, they can significantly inhibit that viral replication and improve the quality of life for people who have HIV infection.

AB The discovery of human immunodeficiency virus (**HIV**) **protease inhibitors** is an example in which pharmacokinetic evaluation was implemented early in the discovery phase to obtain optimal pharmacological and pharmacokinetic properties. Currently, three **HIV protease inhibitors**, saquinavir, indinavir and ritonavir are clinically available. As a family, these **HIV**

protease inhibitors are characterized pharmacologically by their ability to inhibit the viral protease enzyme. Pharmacokinetically, they are quite different due to their dissimilarity in physicochemical properties. Bioavailability appears to be limited with saquinavir, but not with indinavir and ritonavir. Although all three drugs are **metabolized** extensively by cytochrome P-450, saquinavir and indinavir are high clearance drugs while ritonavir is a low clearance drug. Despite their significant differences in elimination clearance, all three HIV proteases are given at high oral doses (600-800 mg) either twice or three times daily. These **HIV protease inhibitors** show superior therapeutic activity and a more favorable safety profile than those reported for the established reverse transcriptase inhibitors. However, the potential for interactions with other drugs **metabolized** by the CYP 3A4 isoform appears to be considerable. In addition, repeated administration of enzyme inducers results in a substantial decrease of plasma concentrations of protease inhibitors. Therefore, co-administration of drugs, such as rifampicin and rifabutin, must be avoided. **HIV protease inhibitors** are promising in the treatment of AIDS. Although they are not a cure, they can significantly inhibit that viral replication and improve the quality of life for people who have HIV infection.

CT EMTAGS: infection (0310); pharmacokinetics (0194); dog (0711); mammal (0738); monkey (0725); human (0888); nonhuman (0777); rat (0733); oral drug administration (0181); review (0001); priority journal (0007)

Medical Descriptors:
*human immunodeficiency virus infection
*pharmacokinetics
enzyme induction
drug design
physical chemistry
drug bioavailability
drug absorption
dog
monkey
drug transport
drug metabolism
drug protein binding
human
nonhuman
rat
oral drug administration
review
priority journal

Drug Descriptors:
*saquinavir: IT, drug interaction
*saquinavir: PK, pharmacokinetics
*indinavir: IT, drug interaction
*indinavir: PK, pharmacokinetics
*ritonavir: IT, drug interaction
*ritonavir: PK, pharmacokinetics
proteinase inhibitor: PK, pharmacokinetics
zidovudine: IT, drug interaction
zalcitabine: IT, drug interaction
rifampicin: IT, drug interaction
rifabutin: EC, endogenous compound

clarithromycin: IT, drug interaction
stavudine: IT, drug interaction
desipramine: IT, drug interaction
nifedipine: IT, drug interaction
terfenadine: IT, drug interaction
dextromethorphan: IT, drug interaction
a 77003: PK, pharmacokinetics
a 80987: PK, pharmacokinetics

RN (saquinavir) 127779-20-8; (indinavir) 150378-17-9, 157810-81-6; (ritonavir) 155213-67-5; (proteinase inhibitor) 37205-61-1; (zidovudine) 30516-87-1; (zalcitabine) 7481-89-2; (rifampicin) 13292-46-1; (rifabutin) 72559-06-9; (clarithromycin) 81103-11-9; (stavudine) 3056-17-5; (desipramine) 50-47-5, 58-28-6; (nifedipine) 21829-25-4; (terfenadine) 50679-08-8; (dextromethorphan) 125-69-9, 125-71-3; (**a 77003**) 134878-17-4

CN **A 77003; A 80987**

L30 ANSWER 2 OF 30 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97159073 EMBASE

TITLE: Hepatic and intestinal **metabolism** of indinavir, an **HIV protease inhibitor**, in rat and human microsomes: Major role of CYP3A.

AUTHOR: Chiba M.; Hensleigh M.; Lin J.H.

CORPORATE SOURCE: Dr. M. Chiba, Merck Research Laboratories, Department of Drug Metabolism, West Point, PA 19486, United States

SOURCE: Biochemical Pharmacology, (1997) 53/8 (1187-1195). Refs: 22
ISSN: 0006-2952 CODEN: BCPCA6

PUBLISHER IDENT.: S 0006-2952(97)00100-7

COUNTRY: United States

DOCUMENT TYPE: Journal

FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The **metabolism** of indinavir, a human immune deficiency virus (**HIV**) **protease inhibitor**, has been characterized extensively in rats and humans. All oxidative **metabolites** found in vivo were formed when indinavir was incubated with NADPH-fortified hepatic and intestinal microsomes obtained from rats and humans. In vitro kinetic studies revealed that V(max)/K(m) values (.mu.L/min/mg protein) in rat and human liver microsomes were approximately 8- and 2-fold greater than those in the intestinal microsomes of the corresponding species (55.8 and 6.7 for the liver and intestine, respectively, in rats; 16.5 and 7.7 for the liver and intestine, respectively, in humans). However, when V(max)/K(m) was scaled up to intrinsic clearance (mL/min/kg body weight), hepatic intrinsic clearance was much greater than the intestinal clearance by 50- to 200-fold. These results suggest that the liver plays a much greater role in first-pass **metabolism** of indinavir than the intestine in both species. Consistently, ketoconazole, a selective inhibitor for CYP3A, and an anti-rat CYP3A1 antibody strongly inhibited hepatic and intestinal **metabolism** of indinavir in both rats and humans, suggesting the involvement of CYP3A isoforms in both organs. Oral treatment of rats with dexamethasone (50 mg/kg/day for 4 days), a potent CYP3A

inducer, increased both hepatic and intestinal **metabolism** of indinavir by a factor of 7 and 3, respectively. Furthermore, indinavir selectively inhibited 6.beta.-hydroxylase activity of testosterone, a GYP3A marker activity, in rat and human liver microsomes; the interactions between testosterone and indinavir were competitive with K(i) values of < 1.0 .mu.M.

TI Hepatic and intestinal **metabolism** of indinavir, an **HIV protease inhibitor**, in rat and human microsomes: Major role of CYP3A.

AB The **metabolism** of indinavir, a human immune deficiency virus (**HIV**) **protease inhibitor**, has been characterized extensively in rats and humans. All oxidative **metabolites** found in vivo were formed when indinavir was incubated with NADPH-fortified hepatic and intestinal microsomes obtained from rats and humans. In vitro kinetic studies revealed that V(max)/K(m) values (.mu.L/min/mg protein) in rat and human liver microsomes were approximately 8- and 2-fold greater than those in the intestinal microsomes of the corresponding species (55.8 and 6.7 for the liver and intestine, respectively, in rats; 16.5 and 7.7 for the liver and intestine, respectively, in humans). However, when V(max)/K(m) was scaled up to intrinsic clearance (mL/min/kg body weight), hepatic intrinsic clearance was much greater than the intestinal clearance by 50- to 200-fold. These results suggest that the liver plays a much greater role in first-pass **metabolism** of indinavir than the intestine in both species. Consistently, ketoconazole, a selective inhibitor for CYP3A, and an anti-rat CYP3A1 antibody strongly inhibited hepatic and intestinal **metabolism** of indinavir in both rats and humans, suggesting the involvement of CYP3A isoforms in both organs. Oral treatment of rats with dexamethasone (50 mg/kg/day for 4 days), a potent CYP3A inducer, increased both hepatic and intestinal **metabolism** of indinavir by a factor of 7 and 3, respectively. Furthermore, indinavir selectively inhibited 6.beta.-hydroxylase activity of testosterone, a GYP3A marker activity, in rat and human liver microsomes; the interactions between testosterone and indinavir were competitive with K(i) values of < 1.0 .mu.M.

CT EMTAGS: pharmacokinetics (0194); digestive system (0935); liver (0946); mammal (0738); human (0888); nonhuman (0777); male (0041); rat (0733); controlled study (0197); human tissue, cells or cell components (0111); animal tissue, cells or cell components (0105); adolescent (0017); article (0060); priority journal (0007); enzyme (0990)

Medical Descriptors:

***drug metabolism**
liver metabolism
intestine
drug oxidation
liver microsome
kinetics
drug clearance
first pass effect
human
nonhuman
male
rat
controlled study
human tissue
animal tissue

adolescent
article
priority journal
Drug Descriptors:
*indinavir: PK, pharmacokinetics
*proteinase inhibitor: PK, pharmacokinetics
reduced nicotinamide adenine dinucleotide phosphate
cytochrome p450 isoenzyme
testosterone
dexamethasone
oxygenase
CN **(1) Mk 639**

L30 ANSWER 3 OF 30 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97092491 EMBASE
TITLE: Indinavir.
AUTHOR: Ohta Y.; Shinkai I.
CORPORATE SOURCE: Japan
SOURCE: Bioorganic and Medicinal Chemistry, (1997) 5/3 (463-464).
ISSN: 0968-0896 CODEN: BMECEP
PUBLISHER IDENT.: S 0968-0896(96)00261-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The IC95 (95% inhibitory concentration) of indinavir was in the range of 25-100 nM. In drug combination studies with the nucleoside analogues zidovudine and didanosine, as well as with an investigational non-nucleoside (L-697,661), indinavir showed synergistic activity in cell culture. Viral resistance was correlated with the accumulation of mutations that resulted in the expression of amino acid substitutions in the viral protease. Eleven amino acid residue positions have been identified. Indinavir was rapidly absorbed in the fasted state. Cross-resistance was noted between indinavir and the protease inhibitor ritonavir. Varying degrees of cross-resistance have been observed between indinavir and other **HIV-protease inhibitors**. Seven **metabolites** have been identified, one glucuronide conjugate and six oxidation **metabolites**. In vitro studies indicate that cytochrome P-450 3A4 (CRY3A4) is the major enzyme responsible for formation of the oxidative **metabolites**. Indinavir has been studied in phase III clinical trials as a monotherapy (dose-escalation) and in combination with zidovudine and with zidovudine + didanosine. The recommended dosage of Crixivan is 800 mg (two 400 mg capsules) orally every 8 h. The dosage is the same whether Crixivan is used alone or in combination with other antiretroviral agents. In an analysis of early clinical trials for safety, nephrolithiasis was the only clinically significant ADR.
AB The IC95 (95% inhibitory concentration) of indinavir was in the range of 25-100 nM. In drug combination studies with the nucleoside analogues zidovudine and didanosine, as well as with an investigational non-nucleoside (L-697,661), indinavir showed synergistic activity in cell culture. Viral resistance was correlated with the accumulation of mutations that resulted in the

expression of amino acid substitutions in the viral protease. Eleven amino acid residue positions have been identified. Indinavir was rapidly absorbed in the fasted state. Cross-resistance was noted between indinavir and the protease inhibitor ritonavir. Varying degrees of cross-resistance have been observed between indinavir and other **HIV-protease inhibitors**. Seven **metabolites** have been identified, one glucuronide conjugate and six oxidation **metabolites**. In vitro studies indicate that cytochrome P-450 3A4 (CRY3A4) is the major enzyme responsible for formation of the oxidative **metabolites**. Indinavir has been studied in phase III clinical trials as a monotherapy (dose-escalation) and in combination with zidovudine and with zidovudine + didanosine. The recommended dosage of Crixivan is 800 mg (two 400 mg capsules) orally every 8 h. The dosage is the same whether Crixivan is used alone or in combination with other antiretroviral agents. In an analysis of early clinical trials for safety, nephrolithiasis was the only clinically significant ADR.

CT EMTAGS: infection (0310); therapy (0160); virus (0761); cell, tissue or organ culture (0103); chemical procedures (0107); heredity (0137); pharmacokinetics (0194); mammal (0738); human (0888); oral drug administration (0181); short survey (0002)
Medical Descriptors:
*antiviral activity
*human immunodeficiency virus infection: DT, drug therapy
*human immunodeficiency virus
in vitro study
cell culture
drug synthesis
drug resistance
mutation
drug metabolism
human
oral drug administration
short survey
Drug Descriptors:
*indinavir: AN, drug analysis
*indinavir: CB, drug combination
*indinavir: CM, drug comparison
*indinavir: DV, drug development
*indinavir: DO, drug dose
*indinavir: DT, drug therapy
*indinavir: PD, pharmacology
*antiretrovirus agent: AN, drug analysis
*antiretrovirus agent: CB, drug combination
*antiretrovirus agent: CM, drug comparison
*antiretrovirus agent: DV, drug development
*antiretrovirus agent: IT, drug interaction
*antiretrovirus agent: PD, pharmacology
zidovudine: CB, drug combination
zidovudine: DT, drug therapy
didanosine: CB, drug combination
didanosine: DT, drug therapy
3 [(4,7 dichloro 2 benzoxazolylmethyl)amino] 5 ethyl 6 methyl 2(1h) pyridone: CB, drug combination
3 [(4,7 dichloro 2 benzoxazolylmethyl)amino] 5 ethyl 6 methyl 2(1h) pyridone: DT, drug therapy
drug metabolite: AN, drug analysis

CN (1) Crixivan; **(2) Mk 639**; (3) L 735524; (4) L 697661

L30 ANSWER 4 OF 30 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97069869 EMBASE
TITLE: Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir.
AUTHOR: Kempf D.J.; Marsh K.C.; Kumar G.; Rodrigues A.D.; Denissen J.F.; McDonald E.; Kukulka M.J.; Hsu A.; Granneman G.R.; Baroldi P.A.; Sun E.; Pizzuti D.; Plattner J.J.; Norbeck D.W.; Leonard J.M.
CORPORATE SOURCE: United States. Dale.J.Kempf@abbott.com
SOURCE: Antimicrobial Agents and Chemotherapy, (1997) 41/3 (654-660).
Refs: 33
ISSN: 0066-4804 CODEN: AMACCQ
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Coadministration with the human immunodeficiency virus (**HIV**) **protease inhibitor** ritonavir was investigated as a method for enhancing the levels of other peptidomimetic **HIV protease inhibitors** in plasma. In rat and human liver microsomes, ritonavir potently inhibited the cytochrome P450 (CYP)- mediated **metabolism** of saquinavir, indinavir, nelfinavir, and **VX-478**. The structural features of ritonavir responsible for CYP binding and inhibition were examined. Coadministration of other protease inhibitors with ritonavir in rats and dogs produced elevated and sustained plasma drug levels 8 to 12 h after a single dose. Drug exposure in rats was elevated by 8- to 46-fold. A >50-fold enhancement of the concentrations of saquinavir in plasma was observed in humans following a single codose of ritonavir (600 mg) and saquinavir (200 mg). These results indicate that ritonavir can favorably alter the pharmacokinetic profiles of other protease inhibitors. Combination regimens of ritonavir and other protease inhibitors may thus play a role in the treatment of HIV infection. Because of potentially substantial drug level increases, however, such combinations require further investigation to establish safe regimens for clinical use.
AB Coadministration with the human immunodeficiency virus (**HIV**) **protease inhibitor** ritonavir was investigated as a method for enhancing the levels of other peptidomimetic **HIV protease inhibitors** in plasma. In rat and human liver microsomes, ritonavir potently inhibited the cytochrome P450 (CYP)- mediated **metabolism** of saquinavir, indinavir, nelfinavir, and **VX-478**. The structural features of ritonavir responsible for CYP binding and inhibition were examined. Coadministration of other protease inhibitors with ritonavir in rats and dogs produced elevated and sustained plasma drug levels 8 to 12 h after a single dose. Drug exposure in rats was elevated by 8- to 46-fold. A >50-fold enhancement of the concentrations of saquinavir in plasma was observed in humans following a single codose of ritonavir (600 mg) and saquinavir (200 mg). These results indicate that ritonavir can

favorably alter the pharmacokinetic profiles of other protease inhibitors. Combination regimens of ritonavir and other protease inhibitors may thus play a role in the treatment of HIV infection. Because of potentially substantial drug level increases, however, such combinations require further investigation to establish safe regimens for clinical use.

CT EMTAGS: virus (0761); infection (0310); therapy (0160); etiology (0135); digestive system (0935); liver (0946); pharmacokinetics (0194); mammal (0738); human (0888); nonhuman (0777); male (0041); female (0042); rat (0733); human experiment (0104); normal human (0800); animal experiment (0112); human tissue, cells or cell components (0111); oral drug administration (0181); article (0060); priority journal (0007)

Medical Descriptors:
*human immunodeficiency virus 1
*human immunodeficiency virus infection: DT, drug therapy
*human immunodeficiency virus infection: ET, etiology
liver microsome
drug metabolism
dose response
drug mixture
drug elimination
drug potentiation
human
nonhuman
male
female
rat
human experiment
normal human
clinical trial
crossover procedure
animal experiment
human tissue
oral drug administration
article
priority journal

Drug Descriptors:
*ritonavir: CT, clinical trial
*ritonavir: CB, drug combination
*ritonavir: DO, drug dose
*ritonavir: IT, drug interaction
*ritonavir: DT, drug therapy
*ritonavir: PK, pharmacokinetics
*ritonavir: PD, pharmacology
*proteinase inhibitor: CT, clinical trial
*proteinase inhibitor: CB, drug combination
*proteinase inhibitor: DO, drug dose
*proteinase inhibitor: IT, drug interaction
*proteinase inhibitor: DT, drug therapy
*proteinase inhibitor: PK, pharmacokinetics
*proteinase inhibitor: PD, pharmacology
saquinavir: CT, clinical trial
saquinavir: CB, drug combination
saquinavir: DO, drug dose
saquinavir: IT, drug interaction
saquinavir: DT, drug therapy
saquinavir: PK, pharmacokinetics

saquinavir: PD, pharmacology
indinavir: CB, drug combination
indinavir: DV, drug development
indinavir: DO, drug dose
indinavir: IT, drug interaction
indinavir: DT, drug therapy
indinavir: PK, pharmacokinetics
indinavir: PD, pharmacology
nelfinavir: CB, drug combination
nelfinavir: DV, drug development
nelfinavir: DO, drug dose
nelfinavir: IT, drug interaction
nelfinavir: DT, drug therapy
nelfinavir: PK, pharmacokinetics
nelfinavir: PD, pharmacology
4 amino n [2 hydroxy 4 phenyl 3 (tetrahydrofuran 3 yloxycarbonylamino)butyl] n isobutylbenzenesulfonamide: CB, drug combination
4 amino n [2 hydroxy 4 phenyl 3 (tetrahydrofuran 3 yloxycarbonylamino)butyl] n isobutylbenzenesulfonamide: DV, drug development
4 amino n [2 hydroxy 4 phenyl 3 (tetrahydrofuran 3 yloxycarbonylamino)butyl] n isobutylbenzenesulfonamide: DO, drug dose
4 amino n [2 hydroxy 4 phenyl 3 (tetrahydrofuran 3 yloxycarbonylamino)butyl] n isobutylbenzenesulfonamide: IT, drug interaction
4 amino n [2 hydroxy 4 phenyl 3 (tetrahydrofuran 3 yloxycarbonylamino)butyl] n isobutylbenzenesulfonamide: DT, drug therapy
4 amino n [2 hydroxy 4 phenyl 3 (tetrahydrofuran 3 yloxycarbonylamino)butyl] n isobutylbenzenesulfonamide: PK, pharmacokinetics
4 amino n [2 hydroxy 4 phenyl 3 (tetrahydrofuran 3 yloxycarbonylamino)butyl] n isobutylbenzenesulfonamide: PD, pharmacology
cytochrome p450
CN **Vx 478**

L30 ANSWER 5 OF 30 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97060069 EMBASE
TITLE: Selective biotransformation of the human immunodeficiency virus protease inhibitor saquinavir by human small-intestinal cytochrome P4503A4: Potential contribution to high first-pass **metabolism**.
AUTHOR: Fitzsimmons M.E.; Collins J.M.
CORPORATE SOURCE: United States
SOURCE: Drug Metabolism and Disposition, (1997) 25/2 (256-266).
Refs: 44
ISSN: 0090-9556 CODEN: DMDSAI
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Saquinavir is a HIV1 protease inhibitor used in the treatment of patients with acquired immunodeficiency syndrome, but its use is limited by low oral bioavailability. The potential of human intestinal tissue to **metabolize** saquinavir was assessed in 17 different human smell-intestinal microsomal preparations. Saquinavir was **metabolized** by human small-intestinal microsomes to numerous mono- and dihydroxylated species with K(M) values of 0.3-0.5 .mu.M. The major **metabolites** M-2 and M-7 were single hydroxylations on the octahydro-2-(1H)-isoquinolinyl and (1,1-dimethylethyl)amino groups, respectively. Ketoconazole and troleandomycin, selective inhibitors of cytochrome P4503A4 (CYP3A4), were potent inhibitors for all oxidative **metabolites** of saquinavir. The cytochrome P450-selective inhibitors furafylline, fluvoxamine, sulfaphenazole, mephenytoin, quinidine, and chlorzoxazone had little inhibitory effect. All saquinavir **metabolites** were highly correlated with testosterone 6.beta.-hydroxylation and with each other. Human hepatic microsomes and recombinant CYP3A4 oxidized saquinavir to the same **metabolic** profile observed with human small-intestinal microsomes. Indinavir, a potent **HIV protease inhibitor** and a substrate for human hepatic CYP3A4, was a comparatively poor substrate for human intestinal microsomes and inhibited the oxidative **metabolism** of saquinavir to all **metabolites** with a K(i) of 0.2 .mu.M. In addition, saquinavir inhibited the human, small- intestinal, microsomal CYP3A4-dependent detoxication pathway of terfenadine to its alcohol **metabolite** with a K(i) value of 0.7 .mu.M. These data indicate that saquinavir is **metabolized** by human intestinal CYP3A4, that this **metabolism** may contribute to its poor oral bioavailability, and that combination therapy with indinavir or other protease inhibitors may attenuate its low relative bioavailability.

TI Selective biotransformation of the human immunodeficiency virus protease inhibitor saquinavir by human small-intestinal cytochrome P4503A4: Potential contribution to high first-pass **metabolism**.

AB Saquinavir is a HIV1 protease inhibitor used in the treatment of patients with acquired immunodeficiency syndrome, but its use is limited by low oral bioavailability. The potential of human intestinal tissue to **metabolize** saquinavir was assessed in 17 different human smell-intestinal microsomal preparations. Saquinavir was **metabolized** by human small-intestinal microsomes to numerous mono- and dihydroxylated species with K(M) values of 0.3-0.5 .mu.M. The major **metabolites** M-2 and M-7 were single hydroxylations on the octahydro-2-(1H)-isoquinolinyl and (1,1-dimethylethyl)amino groups, respectively. Ketoconazole and troleandomycin, selective inhibitors of cytochrome P4503A4 (CYP3A4), were potent inhibitors for all oxidative **metabolites** of saquinavir. The cytochrome P450-selective inhibitors furafylline, fluvoxamine, sulfaphenazole, mephenytoin, quinidine, and chlorzoxazone had little inhibitory effect. All saquinavir **metabolites** were highly correlated with testosterone 6.beta.-hydroxylation and with each other. Human hepatic microsomes and recombinant CYP3A4 oxidized saquinavir to the same **metabolic** profile observed with human small-intestinal microsomes. Indinavir, a potent **HIV protease inhibitor** and a substrate for human hepatic CYP3A4, was a comparatively poor substrate for human intestinal microsomes and

inhibited the oxidative **metabolism** of saquinavir to all **metabolites** with a K(i) of 0.2 .mu.M. In addition, saquinavir inhibited the human, small- intestinal, microsomal CYP3A4-dependent detoxication pathway of terfenadine to its alcohol **metabolite** with a K(i) value of 0.7 .mu.M. These data indicate that saquinavir is **metabolized** by human intestinal CYP3A4, that this **metabolism** may contribute to its poor oral bioavailability, and that combination therapy with indinavir or other protease inhibitors may attenuate its low relative bioavailability.

CT EMTAGS: pharmacokinetics (0194); digestive system (0935); small intestine (0941); liver (0946); mammal (0738); human (0888); controlled study (0197); human tissue, cells or cell components (0111); article (0060); priority journal (0007); enzyme (0990)
Medical Descriptors:
*biotransformation
***drug metabolism**
small intestine
microsome
liver microsome
enzyme inhibition
human
controlled study
human tissue
article
priority journal
Drug Descriptors:
*proteinase inhibitor: PK, pharmacokinetics
*saquinavir: PK, pharmacokinetics
*indinavir: PK, pharmacokinetics
*cytochrome p450 isoenzyme: EC, endogenous compound
*cytochrome p450 inhibitor
alpha naphthoflavone
furafylline
fluvoxamine
quercetin
sulfaphenazole
mephenytoin
quinidine
chlorzoxazone
ketoconazole
troleandomycin
midazolam
cyclosporin a
terfenadine

CN (1) Ro 31 8959; **(2) Mk 639**

L30 ANSWER 6 OF 30 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97033183 EMBASE
TITLE: Indinavir: A pharmacologic and clinical review of a new **HIV protease inhibitor**.
AUTHOR: Lacy M.K.; Abriola K.P.
CORPORATE SOURCE: United States
SOURCE: Connecticut Medicine, (1996) 60/12 (723-727).
Refs: 20
ISSN: 0010-6178 CODEN: CNMEAH
COUNTRY: United States

08687774

DOCUMENT TYPE: Journal
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
TI Indinavir: A pharmacologic and clinical review of a new **HIV protease inhibitor.**
CT EMTAGS: infection (0310); pharmacokinetics (0194); therapy (0160); mammal (0738); human (0888); short survey (0002)
Medical Descriptors:
*human immunodeficiency virus infection
drug information
drug mechanism
drug metabolism
drug indication
human
short survey
Drug Descriptors:
*indinavir: IT, drug interaction
*indinavir: PD, pharmacology
*indinavir: PK, pharmacokinetics
*proteinase inhibitor: PD, pharmacology
*proteinase inhibitor: PK, pharmacokinetics
*proteinase inhibitor: IT, drug interaction
zidovudine: DT, drug therapy
zidovudine: IT, drug interaction
lamivudine: IT, drug interaction
stavudine: IT, drug interaction
stavudine: DT, drug therapy
cimetidine: IT, drug interaction
quinidine: IT, drug interaction
cotrimoxazole: IT, drug interaction
fluconazole: IT, drug interaction
isoniazid: IT, drug interaction
clarithromycin: IT, drug interaction
rifampicin: IT, drug interaction
didanosine: IT, drug interaction
terfenadine: IT, drug interaction
astemizole: IT, drug interaction
cisapride: IT, drug interaction
triazolam: IT, drug interaction
midazolam: IT, drug interaction
ketoconazole: IT, drug interaction
CN (1) Crixivan; **(2) Mk 639**; (3) L 735524

L30 ANSWER 7 OF 30 MEDLINE
ACCESSION NUMBER: 97209067 MEDLINE
TITLE: Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir.
AUTHOR: Kempf D J; Marsh K C; Kumar G; Rodrigues A D; Denissen J F; McDonald E; Kukulka M J; Hsu A; Granneman G R; Baroldi P A; Sun E; Pizzuti D; Plattner J J; Norbeck D W; Leonard J M
CORPORATE SOURCE: Department of Infectious Diseases Research, Abbott Laboratories, Illinois 60064, USA..
Dale.J.Kempf@abbott.com
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1997 Mar) 41

(3) 654-60.
Journal code: 6HK. ISSN: 0066-4804.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 9708
ENTRY WEEK: 19970801

AB Coadministration with the human immunodeficiency virus (**HIV**) **protease inhibitor** ritonavir was investigated as a method for enhancing the levels of other peptidomimetic **HIV protease inhibitors** in plasma. In rat and human liver microsomes, ritonavir potently inhibited the cytochrome P450 (CYP)-mediated **metabolism** of saquinavir, indinavir, nelfinavir, and **VX-478**. The structural features of ritonavir responsible for CYP binding and inhibition were examined. Coadministration of other protease inhibitors with ritonavir in rats and dogs produced elevated and sustained plasma drug levels 8 to 12 h after a single dose. Drug exposure in rats was elevated by 8- to 46-fold. A > 50-fold enhancement of the concentrations of saquinavir in plasma was observed in humans following a single codose of ritonavir (600 mg) and saquinavir (200 mg). These results indicate that ritonavir can favorably alter the pharmacokinetic profiles of other protease inhibitors. Combination regimens of ritonavir and other protease inhibitors may thus play a role in the treatment of HIV infection. Because of potentially substantial drug level increases, however, such combinations require further investigation to establish safe regimens for clinical use.

AB Coadministration with the human immunodeficiency virus (**HIV**) **protease inhibitor** ritonavir was investigated as a method for enhancing the levels of other peptidomimetic **HIV protease inhibitors** in plasma. In rat and human liver microsomes, ritonavir potently inhibited the cytochrome P450 (CYP)-mediated **metabolism** of saquinavir, indinavir, nelfinavir, and **VX-478**. The structural features of ritonavir responsible for CYP binding and inhibition were examined. Coadministration of other protease inhibitors with ritonavir in rats and dogs produced elevated and sustained plasma drug levels 8 to 12 h after a single dose. Drug exposure in rats was elevated by 8- to 46-fold. A > 50-fold enhancement of the concentrations of saquinavir in plasma was observed in humans following a single codose of ritonavir (600 mg) and saquinavir (200 mg). These results indicate that ritonavir can favorably alter the pharmacokinetic profiles of other protease inhibitors. Combination regimens of ritonavir and other protease inhibitors may thus play a role in the treatment of HIV infection. Because of potentially substantial drug level increases, however, such combinations require further investigation to establish safe regimens for clinical use.

CT Check Tags: Animal; Female; Human; Male
*Anti-HIV Agents: PD, pharmacology
Area Under Curve
Cytochrome P-450: AI, antagonists & inhibitors
Cytochrome P-450: ME, metabolism
Dogs
Drug Interactions
HIV Protease Inhibitors: PD, pharmacology

***HIV Protease Inhibitors: PK, pharmacokinetics**
Rats
Rats, Sprague-Dawley
*Ritonavir: PD, pharmacology
CN 0 (Anti-HIV Agents); 0 (**HIV Protease Inhibitors**); 0 (Ritonavir)

L30 ANSWER 8 OF 30 MEDLINE
ACCESSION NUMBER: 97126223 MEDLINE
TITLE: Disposition of indinavir, a potent HIV-1 protease inhibitor, after an oral dose in humans.
AUTHOR: Balani S K; Woolf E J; Hoagland V L; Sturgill M G; Deutsch P J; Yeh K C; Lin J H
CORPORATE SOURCE: Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA.
SOURCE: DRUG METABOLISM AND DISPOSITION, (1996 Dec) 24 (12) 1389-94.
Journal code: EBR. ISSN: 0090-9556.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 9706
ENTRY WEEK: 19970601

AB Indinavir, N-[2(R)-hydroxy-1(S)-indanyl]-5-[2(S)-tertiary-butylaminocarbonyl-4-(3-pyridylmethyl)piperazino]-4(S)-hydroxy-2(R)-phenylmethylpentanamide (L-735,524,**MK-639**, ayl-4- Crixivan), is a potent and specific inhibitor of the HIV-1(3 protease for the treatment of AIDS. Disposition of [14C]indinavir was investigated in six healthy subjects after single oral administration of 400 mg. AUC, Cmax, and Tmax values for indinavir were 492 microM x min, 4.7 microM, and 50 min, respectively. The AUC value for the total radioactivity in plasma was 1.9 times higher than that of indinavir, indicating the presence of **metabolites**. The major excretory route was through feces, and the minor through urine. Mean recovery of radioactivity in the feces was 83.4%. In the urine, mean recoveries of the total radioactivity and unchanged indinavir were 18.7% and 11.0% of the dose, respectively. HPLC radioactivity and LC-MS/MS analyses of urine showed the presence of indinavir and low levels of quaternary pyridine N-glucuronide (M1), 2',3'-trans-dihydroxyindanylpyridine N-oxide (M2), 2',3'-trans-dihydroxyindan (M3) and pyridine N-oxide (M4a) analogs, and despyridylmethyl analogs of M3 (M5) and indinavir (M6). M5 and M6 were the major **metabolites** in urine. The **metabolic** profile in plasma was similar to that in urine. Quantitatively, the **metabolites** in feces accounted for >47% of the dose, which along with the urinary excretion of approximately 19%, suggested that the absorption of the drug was appreciable. In the feces, radioactivity was predominantly due to M3, M5, M6, and the parent compound. Thus, in urine and feces, the prominent **metabolic** pathways were oxidations and oxidative N-dealkylations. Excretion of the quaternary N-glucuronide **metabolite** in the urine, which is a minor **metabolite** in human, was specific to primates.
AB Indinavir, N-[2(R)-hydroxy-1(S)-indanyl]-5-[2(S)-tertiary-butylaminocarbonyl-4-(3-pyridylmethyl)piperazino]-4(S)-hydroxy-2(R)-phenylmethylpentanamide (L-735,524,**MK-**

639, ayl-4- Crixivan), is a potent and specific inhibitor of the HIV-1(3 protease for the treatment of AIDS. Disposition of [14C]indinavir was investigated in six healthy subjects after single oral administration of 400 mg. AUC, Cmax, and Tmax values for indinavir were 492 microM x min, 4.7 microM, and 50 min, respectively. The AUC value for the total radioactivity in plasma was 1.9 times higher than that of indinavir, indicating the presence of **metabolites**. The major excretory route was through feces, and the minor through urine. Mean recovery of radioactivity in the feces was 83.4%. In the urine, mean recoveries of the total radioactivity and unchanged indinavir were 18.7% and 11.0% of the dose, respectively. HPLC radioactivity and LC-MS/MS analyses of urine showed the presence of indinavir and low levels of quaternary pyridine N-glucuronide (M1), 2',3'-trans-dihydroxyindanylpyridine N-oxide (M2), 2',3'-trans-dihydroxyindan (M3) and pyridine N-oxide (M4a) analogs, and despyridylmethyl analogs of M3 (M5) and indinavir (M6). M5 and M6 were the major **metabolites** in urine. The **metabolic** profile in plasma was similar to that in urine. Quantitatively, the **metabolites** in feces accounted for >47% of the dose, which along with the urinary excretion of approximately 19%, suggested that the absorption of the drug was appreciable. In the feces, radioactivity was predominantly due to M3, M5, M6, and the parent compound. Thus, in urine and feces, the prominent **metabolic** pathways were oxidations and oxidative N-dealkylations. Excretion of the quaternary N-glucuronide **metabolite** in the urine, which is a minor **metabolite** in human, was specific to primates.

CT Check Tags: Animal; Female; Human; Male
Adult
Area Under Curve
Bile: ME, metabolism
Biotransformation
Chromatography, High Pressure Liquid
Chromatography, Liquid
Dogs
Feces: CH, chemistry
***HIV Protease Inhibitors: PK, pharmacokinetics**
HIV Protease Inhibitors: UR, urine
*HIV-1: EN, enzymology
*Indinavir: PK, pharmacokinetics
Indinavir: UR, urine
Rats
Rats, Sprague-Dawley
Species Specificity
Spectrophotometry, Ultraviolet
Spectrum Analysis, Mass

CN 0 (**HIV Protease Inhibitors**)

L30 ANSWER 9 OF 30 MEDLINE
ACCESSION NUMBER: 97126022 MEDLINE
TITLE: Genetic correlates of in vivo viral resistance to indinavir, a human immunodeficiency virus type 1 protease inhibitor.
AUTHOR: Condra J H; Holder D J; Schleif W A; Blahy O M; Danovich R M; Gabryelski L J; Graham D J; Laird D; Quintero J C; Rhodes A; Robbins H L; Roth E; Shivaprakash M; Yang T; Chodakewitz J A; Deutsch P J; Leavitt R Y; Massari F E; Mellors J W; Squires K E;

08687774

Steigbigel R T; Teppler H; Emini E A
CORPORATE SOURCE: Department of Antiviral Research, Merck Research Laboratories, West Point, Pennsylvania 19486, USA.. jon_condra@merck.com
SOURCE: JOURNAL OF VIROLOGY, (1996 Dec) 70 (12) 8270-6.
Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-U71606; GENBANK-U72026
ENTRY MONTH: 9703
ENTRY WEEK: 19970304
AB Indinavir (IDV) (also called CRIXIVAN, **MK-639**, or L-735,524) is a potent and selective inhibitor of the human immunodeficiency virus type 1 (HIV-1) protease. During early clinical trials, in which patients initiated therapy with suboptimal dosages of IDV, we monitored the emergence of viral resistance to the inhibitor by genotypic and phenotypic characterization of primary HIV-1 isolates. Development of resistance coincided with variable patterns of multiple substitutions among at least 11 protease amino acid residues. No single substitution was present in all resistant isolates, indicating that resistance evolves through multiple genetic pathways. Despite this complexity, all of 29 resistant isolates tested exhibited alteration of residues M-46 (to I or L) and/or V-82 (to A, F, or T), suggesting that screening of these residues may be useful in predicting the emergence of resistance. We also extended our previous finding that IDV-resistant viral variants exhibit various patterns of cross-resistance to a diverse panel of HIV-1 protease inhibitors. Finally, we noted an association between the number of protease amino acid substitutions and the observed level of IDV resistance. No single substitution or pair of substitutions tested gave rise to measurable viral resistance to IDV. The evolution of this resistance was found to be cumulative, indicating the need for ongoing viral replication in this process. These observations strongly suggest that therapy should be initiated with the most efficacious regimen available, both to suppress viral spread and to inhibit the replication that is required for the evolution of resistance.
AB Indinavir (IDV) (also called CRIXIVAN, **MK-639**, or L-735,524) is a potent and selective inhibitor of the human immunodeficiency virus type 1 (HIV-1) protease. During early clinical trials, in which patients initiated therapy with suboptimal dosages of IDV, we monitored the emergence of viral resistance to the inhibitor by genotypic and phenotypic characterization of primary HIV-1 isolates. Development of resistance coincided with variable patterns of multiple substitutions among at least 11 protease amino acid residues. No single substitution was present in all resistant isolates, indicating that resistance evolves through multiple genetic pathways. Despite this complexity, all of 29 resistant isolates tested exhibited alteration of residues M-46 (to I or L) and/or V-82 (to A, F, or T), suggesting that screening of these residues may be useful in predicting the emergence of resistance. We also extended our previous finding that IDV-resistant viral variants exhibit various patterns of cross-resistance to a diverse panel of HIV-1 protease inhibitors. Finally, we noted an association between the number of protease amino acid substitutions and the observed level of IDV resistance. No single substitution or

pair of substitutions tested gave rise to measurable viral resistance to IDV. The evolution of this resistance was found to be cumulative, indicating the need for ongoing viral replication in this process. These observations strongly suggest that therapy should be initiated with the most efficacious regimen available, both to suppress viral spread and to inhibit the replication that is required for the evolution of resistance.

CT Check Tags: Human
Base Sequence
Drug Resistance, Microbial
DNA, Viral
Genotype
Hela Cells
HIV Infections: DT, drug therapy
*HIV Infections: VI, virology
HIV Protease: CH, chemistry
***HIV Protease: ME, metabolism**
***HIV Protease Inhibitors: PD, pharmacology**
HIV-1: CL, classification
*HIV-1: DE, drug effects
HIV-1: EN, enzymology
HIV-1: IP, isolation & purification
*Indinavir: PD, pharmacology
Molecular Sequence Data
Phenotype
Variation (Genetics)

CN EC 3.4.23.- (HIV Protease); 0 (DNA, Viral); 0 (**HIV Protease Inhibitors**)

L30 ANSWER 10 OF 30 MEDLINE

ACCESSION NUMBER: 97125958 MEDLINE

TITLE: Human immunodeficiency virus. Mutations in the viral protease that confer resistance to saquinavir increase the dissociation rate constant of the protease-saquinavir complex.

AUTHOR: Maschera B; Darby G; Palu G; Wright L L; Tisdale M; Myers R; Blair E D; Furfine E S

CORPORATE SOURCE: Department of Virology, Glaxo Wellcome, Stevenage SG1 2NY, United Kingdom.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec 27) 271 (52) 33231-5.
Journal code: HIV. ISSN: 0021-9258.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 9704

ENTRY WEEK: 19970401

AB Mutations in the human immunodeficiency virus (HIV) protease (L90M, G48V, and L90M/G48V) arise when HIV is passaged in the presence of the **HIV protease inhibitor** saquinavir.
These mutations yield a virus with less sensitivity to the drug (L90M > G48V >> L90M/G48V). L90M, G48V, and L90M/G48V proteases have 1/20, 1/160, and 1/1000 the affinity for saquinavir compared to WT protease, respectively. Therefore, the affinity of mutant protease for saquinavir decreased as the sensitivity of the virus to saquinavir decreased. Association rate constants for WT and mutant proteases with saquinavir were similar, ranging from 2 to 4 x 10(7)

M-1 s-1. In contrast, the dissociation rate constants for WT, L90M, G48V, and L90M/G48V proteases complexed with saquinavir were 0.0014, 0.019, 0.128, and 0. 54 s-1, respectively. This indicated that the reduced affinity for mutant proteases and saquinavir is primarily the result of larger dissociation rate constants. The increased dissociation rate constants may be the result of a decrease in the internal equilibrium between the bound inhibitor with the protease flaps up and the bound inhibitor with the flaps down. Interestingly, the affinity of these mutant proteases for **VX-478** , ABT-538, AG-1343, or L-735,524 was not reduced as much as that for saquinavir. Finally, the catalytic constants of WT and mutant proteases were determined for eight small peptide substrates that mimic the viral cleavage sites in vivo. WT and L90M proteases had similar catalytic constants for these substrates. In contrast, G48V and L90M/G48V proteases had catalytic efficiency (kcat/Km) values with TLNF-PISP, RKIL-FLDG, and AETF-YVDG that were 1/10 to 1/20 the value of WT protease. The decreased catalytic efficiencies were primarily the result of increased Km values. Thus, mutations in the protease decrease the affinity of the enzyme for saquinavir and the catalytic efficiency with peptide substrates.

AB Mutations in the human immunodeficiency virus (HIV) protease (L90M, G48V, and L90M/G48V) arise when HIV is passaged in the presence of the **HIV protease inhibitor** saquinavir.
These mutations yield a virus with less sensitivity to the drug (L90M > G48V >> L90M/G48V). L90M, G48V, and L90M/G48V proteases have 1/20, 1/160, and 1/1000 the affinity for saquinavir compared to WT protease, respectively. Therefore, the affinity of mutant protease for saquinavir decreased as the sensitivity of the virus to saquinavir decreased. Association rate constants for WT and mutant proteases with saquinavir were similar, ranging from 2 to 4 x 10(7) M-1 s-1. In contrast, the dissociation rate constants for WT, L90M, G48V, and L90M/G48V proteases complexed with saquinavir were 0.0014, 0.019, 0.128, and 0. 54 s-1, respectively. This indicated that the reduced affinity for mutant proteases and saquinavir is primarily the result of larger dissociation rate constants. The increased dissociation rate constants may be the result of a decrease in the internal equilibrium between the bound inhibitor with the protease flaps up and the bound inhibitor with the flaps down. Interestingly, the affinity of these mutant proteases for **VX-478** , ABT-538, AG-1343, or L-735,524 was not reduced as much as that for saquinavir. Finally, the catalytic constants of WT and mutant proteases were determined for eight small peptide substrates that mimic the viral cleavage sites in vivo. WT and L90M proteases had similar catalytic constants for these substrates. In contrast, G48V and L90M/G48V proteases had catalytic efficiency (kcat/Km) values with TLNF-PISP, RKIL-FLDG, and AETF-YVDG that were 1/10 to 1/20 the value of WT protease. The decreased catalytic efficiencies were primarily the result of increased Km values. Thus, mutations in the protease decrease the affinity of the enzyme for saquinavir and the catalytic efficiency with peptide substrates.

CT Check Tags: Human
Antiviral Agents: ME, metabolism
Drug Resistance, Microbial
*HIV Protease: GE, genetics
HIV Protease: ME, metabolism
HIV Protease Inhibitors: ME, metabolism
Indinavir: ME, metabolism
Isoquinolines: ME, metabolism

Kinetics
Mutagenesis
Ritonavir: ME, metabolism
Saquinavir: ME, metabolism
*Saquinavir: TU, therapeutic use
Sulfonamides: ME, metabolism
Sulfonic Acids: ME, metabolism
CN EC 3.4.23.- (HIV Protease); 0 (Antiviral Agents); 0 (AG 1343); 0 (**HIV Protease Inhibitors**); 0 (Isoquinolines); 0 (Ritonavir); 0 (Sulfonamides); 0 (Sulfonic Acids); 0 (**VX 478**)

L30 ANSWER 11 OF 30 MEDLINE
ACCESSION NUMBER: 97112989 MEDLINE
TITLE: Mutational anatomy of an HIV-1 protease variant conferring cross-resistance to protease inhibitors in clinical trials. Compensatory modulations of binding and activity.
AUTHOR: Schock H B; Garsky V M; Kuo L C
CORPORATE SOURCE: Department of Antiviral Research, Merck Research Laboratories, West Point, Pennsylvania 19486, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec 13) 271 (50) 31957-63.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 9703
ENTRY WEEK: 19970304
AB Site-specific substitutions of as few as four amino acids (M46I/L63P/V82T/I84V) of the human immunodeficiency virus type 1 (HIV-1) protease engenders cross-resistance to a panel of protease inhibitors that are either in clinical trials or have recently been approved for HIV therapy (Condra, J. H., Schleif, W. A., Blahy, O. M. , Gadryelski, L. J., Graham, D. J., Quintero, J. C., Rhodes, A., Robbins, H. L., Roth, E., Shivaprakash, M., Titus, D., Yang, T., Teppler, H., Squires, K. E., Deutsch, P. J., and Emini, E. A. (1995) Nature 374, 569-571). These four substitutions are among the prominent mutations found in primary HIV isolates obtained from patients undergoing therapy with several protease inhibitors. Two of these mutations (V82T/I84V) are located in, while the other two (M46I/L63P) are away from, the binding cleft of the enzyme. The functional role of these mutations has now been delineated in terms of their influence on the binding affinity and catalytic efficiency of the protease. We have found that the double substitutions of M46I and L63P do not affect binding but instead endow the enzyme with a catalytic efficiency significantly exceeding (110-360%) that of the wild-type enzyme. In contrast, the double substitutions of V82T and I84V are detrimental to the ability of the protease to bind and, thereby, to catalyze. When combined, the four amino acid replacements institute in the protease resistance against inhibitors and a significantly higher catalytic activity than one containing only mutations in its active site. The results suggest that in raising drug resistance, these four site-specific mutations of the protease are compensatory in function; those in the active site diminish equilibrium binding (by increasing Ki), and those away from the active site enhance catalysis (by increasing kcat/KM). This

conclusion is further supported by energy estimates in that the Gibbs free energies of binding and catalysis for the quadruple mutant are quantitatively dictated by those of the double mutants.

CT Check Tags: Human
Clinical Trials
Fusion Proteins, gag-pol: ME, metabolism
Hydrolysis
HIV Protease: CH, chemistry
*HIV Protease: GE, genetics
***HIV Protease Inhibitors: PD, pharmacology**
Indinavir: PD, pharmacology
Kinetics
Mutagenesis
Ritonavir: PD, pharmacology
Sulfonamides: PD, pharmacology

CN EC 3.4.23.- (HIV Protease); 0 (Fusion Proteins, gag-pol); 0 (**HIV Protease Inhibitors**); 0 (Ritonavir); 0 (Sulfonamides); 0 (**VX 478**)

L30 ANSWER 12 OF 30 MEDLINE

ACCESSION NUMBER: 97046545 MEDLINE
TITLE: Ritonavir.
AUTHOR: Lea A P; Faulds D
CORPORATE SOURCE: Adis International Limited, Auckland, New Zealand.
SOURCE: DRUGS, (1996 Oct) 52 (4) 541-6; discussion 547-8.
Ref: 37
Journal code: EC2. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 9704
ENTRY WEEK: 19970401

AB Ritonavir is a protease inhibitor with an HIV-1 resistance profile similar to that of indinavir, but different from that of saquinavir. Ritonavir has good oral bioavailability, and may increase the bioavailability of other protease inhibitors including saquinavir, nelfinavir, indinavir and **VX-478**. Clinically significant drug interactions have been predicted between ritonavir and a range of medications. In patients with HIV-1 infection, ritonavir markedly reduced viral load within 2 weeks of treatment onset and also increased CD4+ cell counts. In a large placebo-controlled trial in patients with advanced HIV infection, the addition of ritonavir to existing therapy reduced the risk of mortality by 43% and clinical progression by 56% after 6.1 months. Triple therapy with ritonavir plus zidovudine, in combination with lamivudine or zalcitabine, reduced HIV viraemia to below detectable levels in most patients with acute, and some patients with advanced HIV infection in 2 small trials. Early results suggest combination therapy with ritonavir and saquinavir increases CD4+ cell counts and decreases HIV RNA levels in patients with previously untreated HIV infection.

AB Ritonavir is a protease inhibitor with an HIV-1 resistance profile similar to that of indinavir, but different from that of saquinavir. Ritonavir has good oral bioavailability, and may increase the bioavailability of other protease inhibitors including saquinavir,

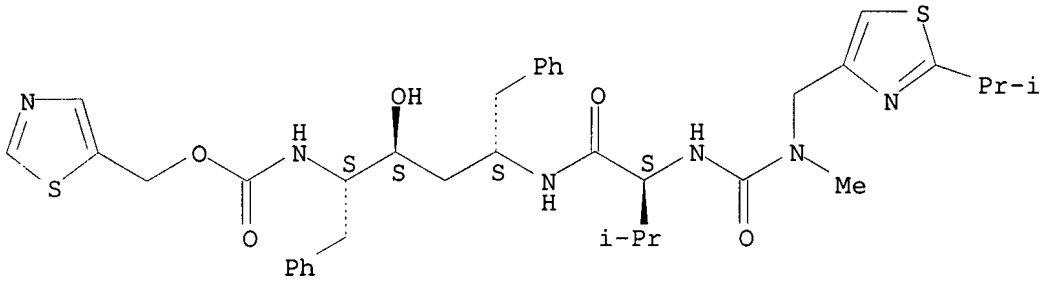
4-14-97

```
=> s ritonavir/cn
L2            1 RITONAVIR/CN

=> d l2

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 1997 ACS
RN   155213-67-5  REGISTRY
CN   2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-
     methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-
     bis(phenylmethyl)-, 5-thiazolylmethyl ester, [5S-
     (5R*,8R*,10R*,11R*)]- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   A 84538
CN   Abbott 84538
CN   ABT 538
CN   Norvir
CN   Ritonavir
FS   STEREOSEARCH
MF   C37 H48 N6 O5 S2
CI   COM
SR   CAS Registry Services
LC   STN Files:   BIOBUSINESS, BIOSIS, CA, CAPLUS, CEN, CHEMLIST, CIN,
       DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, PHAR,
       PROMT, TOXLINE, TOXLIT, USAN, USPATFULL

Absolute stereochemistry.
```



35 REFERENCES IN FILE CA (1967 TO DATE)
35 REFERENCES IN FILE CAPLUS (1967 TO DATE)

```
=> s l3 and cyclosporine
          4007 CYCLOSPORINE
L5           1 L3 AND CYCLOSPORINE

=> d bib ab

L5   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 1997 ACS
AN   1997:184660  CAPLUS
DN   126:166463
TI   Use of ritonavir (ABT-538) for improving the pharmacokinetics of
     drugs metabolized by cytochrome P450 in a method of treating aids
IN   Norbeck, Daniel W.; Kempf, Dale J.; Leonard, John M.; Bertz, Richard
     J.
PA   Abbott Laboratories, USA
SO   PCT Int. Appl., 28 pp.
     CODEN: PIXXD2
PI   WO 9701349 A1  970116
DS   W:  AU, CA, IS, JP, KR, MX
     RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,
         SE
AI   WO 96-US11015  960628
PRAI US 95-654  950629
     US 95-3849  950915
DT   Patent
LA   English
AB   A method is disclosed for improving the pharmacokinetics of a drug
     which is metabolized by cytochrome P 450 monooxygenase by use of
     ritonavir.  HIV inhibitory action is also claimed by combinations of
     ritonavir with protease inhibitors whose pharmacokinetics are
     modulated by ritanovir via its inhibitory action on cytochrome P
     450.
```

```
=> s wo9414436/pn
L1            1 WO9414436/PN
                (WO9414436/PN)

=> d ibib ab

L1   ANSWER 1 OF 1  WPIDS   COPYRIGHT 1997 DERWENT INFORMATION LTD
ACCESSION NUMBER:      94-234319 [28]   WPIDS
CROSS REFERENCE:       90-377452 [51];  92-176578 [22];  92-348620 [42];
                       93-350874 [44];  93-386428 [48];  94-357440 [44]
DOC. NO. CPI:          C94-106528
TITLE:                 New di heterocyclyl-substd. carbonate cpds. - used
                       as HIV protease inhibiting anti-retroviral agents
                       esp. for treating AIDS.
DERWENT CLASS:         B03
INVENTOR(S):           KEMPF, D J; NORBECK, D W; SHAM, H L; ZHAO, C;
                       COOPER, A J; HAIGHT, A R; RENO, D S; SOWIN, T J;
                       ALLEN, M S; COPPER, A J; TIEN, J J
PATENT ASSIGNEE(S):    (ABBO) ABBOTT LAB
COUNTRY COUNT:         23
PATENT INFORMATION:

     PATENT NO KIND DATE   WEEK    LA   PG
     ----------------------------------------
     WO 9414436  A1 940707 (9428)* EN  194        <--
        RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
         W: AU CA JP KR
     AU 9459546  A  940719 (9439)
     AU 659575   B  950518 (9528)
     IL 108126   A  950330 (9530)
     AU 9514927  A  950615 (9532)
     EP 674513   A1 951004 (9544)  EN
         R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
     EP 674513   A4 951025 (9620)
     US 5539122  A  960723 (9635)       52
     US 5541206  A  960730 (9636)      106
     EP 727419   A2 960821 (9638)  EN   84
         R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
   ✓ US 5552558  A  960903 (9641)       56
     EP 674513   B1 960925 (9643)  EN  112
         R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
     ES 2088839  T1 961001 (9645)
     CA 2135890  C  960827 (9647)
    ✓US 5565418  A  961015 (9647)       52
     JP 08505844 W  960625 (9648)      217
     DE 69305093 E  961031 (9649)
     EP 727419   A3 961030 (9649)
     US 5580984  A  961203 (9703)       52
     US 5583232  A  961210 (9704)       58
     US 5583233  A  961210 (9704)       55
     US 5591860  A  970107 (9708)       53
     US 5597927  A  970128 (9710)       55
     US 5597928  A  970128 (9710)       56
     ES 2088839  T3 970201 (9712)
     US 5608072  A  970304 (9715)       60

APPLICATION DETAILS:

     PATENT NO  KIND                 APPLICATION     DATE
```

WO 9414436	A1			WO 93-US12326	931216
AU 9459546	A			AU 94-59546	931216
AU 659575	B			AU 94-59546	931216
IL 108126	A			IL 93-108126	931221
AU 9514927	A	Div ex		AU 94-59546	931216
				AU 95-14927	950320
EP 674513	A1			WO 93-US12326	931216
				EP 94-905429	931216
EP 674513	A4			EP 94-905429	
US 5539122	A	CIP of		US 89-355945	890523
		CIP of		US 89-405604	890908
		CIP of		US 89-456124	891222
		CIP of		US 90-518730	900509
		CIP of		US 90-616170	901120
		CIP of		US 91-746020	910815
		CIP of		US 91-777626	911023
		CIP of		US 92-998114	921229
		Div ex		US 93-158587	931202
				US 95-410996	950327
US 5541206	A	CIP of		US 89-355945	890523
		CIP of		US 89-405604	890908
		CIP of		US 89-456124	891222
		CIP of		US 90-518730	900509
		CIP of		US 90-616170	901120
		CIP of		US 91-746020	910815
		CIP of		US 91-777626	911023
		CIP of		US 92-998114	921229
		Cont of		US 93-158587	931202
				US 95-423387	950425
EP 727419	A2	Div ex		EP 94-905429	931216
				EP 96-106301	931216
US 5552558	A	CIP of		US 89-355945	890523
		CIP of		US 89-405604	890908
		CIP of		US 89-456124	891222
		CIP of		US 90-518730	900509
		CIP of		US 90-616170	901120
		CIP of		US 91-746020	910815
		CIP of		US 91-777626	911023
		CIP of		US 92-998114	921229
		Div ex		US 93-158587	931202
				US 95-411032	950327
EP 674513	B1			WO 93-US12326	931216
				EP 94-905429	931216
ES 2088839	T1			EP 94-905429	931216
CA 2135890	C			CA 93-2135890	931216
US 5565418	A	CIP of		US 89-355945	890523
		CIP of		US 89-405604	890908
		CIP of		US 89-456124	891222
		CIP of		US 90-518730	900509
		CIP of		US 90-616170	901120
		CIP of		US 91-746020	910815
		CIP of		US 91-777626	911023
		CIP of		US 92-998114	921229
		Div ex		US 93-158587	931202
				US 95-417304	950405
JP 08505844	W			WO 93-US12326	931216
				JP 94-515323	931216
DE 69305093	E			DE 93-605093	931216
				WO 93-US12326	931216
				EP 94-905429	931216
EP 727419	A3	Div ex		EP 94-905429	931216
				EP 96-106301	931216
US 5580984	A	CIP of		US 89-355945	890523
		CIP of		US 89-405604	890908
		CIP of		US 89-456124	891222

		CIP of	US	90-518730	900509
		CIP of	US	90-616170	901120
		CIP of	US	91-746020	910815
		CIP of	US	91-777626	911023
		CIP of	US	92-998114	921229
		Div ex	US	93-158587	931202
			US	95-412253	950328
US 5583232	A	CIP of	US	89-355945	890523
		CIP of	US	89-405604	890908
		CIP of	US	89-456124	891222
		CIP of	US	90-518730	900509
		CIP of	US	90-616170	901120
		CIP of	US	91-746020	910815
		CIP of	US	91-777626	911023
		CIP of	US	92-998114	921229
		Div ex	US	93-158587	931202
			US	95-412821	950329
US 5583233	A	CIP of	US	89-355945	890523
		CIP of	US	89-405604	890908
		CIP of	US	89-456124	891222
		CIP of	US	90-518730	900509
		CIP of	US	90-616170	901120
		CIP of	US	91-746020	910815
		CIP of	US	91-777626	911023
		CIP of	US	92-998114	921229
		Div ex	US	93-158587	931202
			US	95-413290	950330
US 5591860	A	CIP of	US	89-355945	890523
		CIP of	US	89-405604	890908
		CIP of	US	89-456124	891222
		CIP of	US	90-518730	900509
		CIP of	US	90-616170	901120
		CIP of	US	91-746020	910815
		CIP of	US	91-777626	911023
		CIP of	US	92-998114	921229
		Div ex	US	93-158587	931202
			US	95-416272	950404
US 5597927	A	CIP of	US	89-355945	890523
		CIP of	US	89-405604	890908
		CIP of	US	89-456124	891222
		CIP of	US	90-518730	900509
		CIP of	US	90-616170	901120
		CIP of	US	91-746020	910815
		CIP of	US	91-777626	911023
		CIP of	US	92-998114	921229
		Div ex	US	93-158587	931202
			US	95-412438	950329
US 5597928	A	CIP of	US	89-355945	890523
		CIP of	US	89-405604	890908
		CIP of	US	89-456124	891222
		CIP of	US	90-518730	900509
		CIP of	US	90-616170	901120
		CIP of	US	91-746020	910815
		CIP of	US	91-777626	911023
		CIP of	US	92-998114	921229
		Div ex	US	93-158587	931202
			US	95-416607	950404
ES 2088839	T3		EP	94-905429	931216
US 5608072	A	CIP of	US	89-355945	890523
		CIP of	US	89-405604	890908
		CIP of	US	89-456124	891222
		CIP of	US	90-518730	900509
		CIP of	US	90-616170	901120
		CIP of	US	91-746020	910815
		CIP of	US	91-777626	911023
		CIP of	US	92-998114	921229

Div ex[redacted] US 93-158587 931202
US 95-416259 950404[redacted]

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9459546	A	Based on	WO 9414436
AU 659575	B	Previous Publ.	AU 9459546
		Based on	WO 9414436
EP 674513	A1	Based on	WO 9414436
US 5539122	A	CIP of	US 5142056
US 5541206	A	CIP of	US 5142056
US 5552558	A	CIP of	US 5142056
EP 674513	B1	Based on	WO 9414436
ES 2088839	T1	Based on	EP 674513
US 5565418	A	CIP of	US 5142056
JP 08505844	W	Based on	WO 9414436
DE 69305093	E	Based on	EP 674513
		Based on	WO 9414436
US 5580984	A	CIP of	US 5142056
US 5583232	A	CIP of	US 5142056
US 5583233	A	CIP of	US 5142056
US 5591860	A	CIP of	US 5142056
US 5597927	A	CIP of	US 5142056
US 5597928	A	CIP of	US 5142056
ES 2088839	T3	Based on	EP 674513
US 5608072	A	CIP of	US 5142056

PRIORITY APPLN. INFO: US 93-158587 931202; US 92-998114 921229; US 89-355945 890523; US 89-405604 890908; US 89-456124 891222; US 90-518730 900509; US 90-616170 901120; US 91-746020 910815; US 91-777626 911023; US 95-410996 950327; US 95-423387 950425; US 95-411032 950327; US 95-417304 950405; US 95-412253 950328; US 95-412821 950329; US 95-413290 950330; US 95-416272 950404; US 95-412438 950329; US 95-416607 950404; US 95-416259 950404

AB WO 9414436 A UPAB: 960918
O-(Heterocyclyl-alkyl)- N-(Heterocyclyl-substd. carbonylamino-alkyl)-carbamates of formula (I) and their salts, esters and prodrugs are new. R1 = thiazolyl, oxazolyl, isoxazolyl or isothiazolyl, all mono-substd. by Q; Q = lower alkyl, lower alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, Het, Het-alkyl, alkoxyalkyl, thioalkoxyalkyl, alkylamino, dialkylamino, phenyl (opt. substd. by halo, lower alkyl, OH, alkoxy or thioalkoxy), phenyl alkyl (opt. ring-substd. as for phenyl), dialkylaminoalkyl, alkoxy or thioalkoxy; Het = aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl or pyrazinyl (all opt. substd. by halo, lower alkyl, OH, alkoxy or thioalkoxy); n = 1-3; R2 = H or lower alkyl; R3 = lower alkyl; R4, R4a = phenyl, thiazolyl or oxazolyl (all opt. substd. by halo, lower alkyl, OH, alkoxy or thioalkoxy); R6 = H or lower alkoxy; R7 = chiazolyl, oxazolyl, isoxazolyl, or isothiazolyl, (all opt. substd. by lower alkyl); one of X, Y = H and the other = OH; or X = Y = OH Z = direct bond, O, S, CH2 or NR8; R8 = lower alkyl, cycloalkyl, OH or NHR8a; R8a = H, lower alkyl or N-protecting gp.; provided that, in cpds. where only one of X and Y = OH, X = H and Y = OH when R7 is unsubstd. and either Z = NR8 or R3 = Me lower = up to 6C.

USE/ADVANTAGE - (I) are retroviral protease inhibitors, esp. HIV protease inhibitor (claimed), effective in vitro or in vivo. (I) inhibit retroviruses, esp. HIV, in vivo and are useful for treatment or prophylaxis of diseases caused by retroviruses, esp. AIDS or HIV

infection. (I) may be free of the adverse effects of other anti-AIDS agents, e.g. low platelet count, renal toxicity and bone marrow cytopenia.

Dwg.0/0